

INFORMACIÓN ADICIONAL

¿Qué es una enfermedad cardiovascular?

Término para hablar de enfermedades con el corazón y los vasos sanguíneos. Esta afección ocurre cuando la grasa y el colesterol se acumulan en las paredes del vaso sanguíneo (arteria). Esta acumulación se llama placa. Con el tiempo, la placa puede estrechar los vasos sanguíneos y causar problemas en todo el cuerpo. Si una arteria resulta obstruida, esto puede llevar a que se presente un ataque cardíaco o un accidente cerebrovascular.

INFORMACIÓN DEL KIT BE FREE

El KIT de Be Free trae los 4 suplementos en un solo paquete. Cada suplemento dentro de la caja trae tratamiento para 20 días cada uno. Tiene un precio de 2,100 pesos.

PRODUCTOS:

Be Free W 1

Descripción: Suplemento alimenticio a base de extracto de Satsuma Mandarina y extracto de Granada, diseñado para reducir las várices y mejorar la microcirculación.

El activo principal es la satsuma mandarina, es una fruta japonesa que aporta una gran cantidad de vitamina C, la cual ayuda en la fabricación de colágeno, un nutriente necesario para la reparación de los vasos sanguíneos.

Beneficios:

Aumenta el flujo sanguíneo

Reduce la inflamación

Alivia el dolor, sensación de pesadez y calambres en las piernas.

Mejora la microcirculación

Modo de Uso: 2 cápsulas al día, antes del desayuno, con agua.

Precio: \$550 pesos

Link de compra: <https://mireipharma.com.mx/products/w1-vc-60-capsulas>

Be Free W 2

Descripción: Suplemento alimenticio de espirulina y extracto de Granada, enfocado en el control de peso, equilibrio metabólico y balance hormonal.

El activo principal es la espirulina, es un alga que favorece la pérdida de peso al actuar como inhibidora del apetito y ayuda a reducir el tejido adiposo, debido a que inhibe una enzima que interviene en el proceso de producción de ácidos grasos en el organismo y a su acción antiinflamatoria.

Beneficios:

Reduce la grasa visceral

Conserva el tejido magro

Mejora la saciedad

Quemador de grasa

Reduce síntomas climatéricos

Modo de Uso: 1 ampolla al día, diluida en 200 mili litros de jugo, después del desayuno.

Precio: \$650 pesos

Link de compra: <https://mireipharma.com.mx/products/w2-mb-30-ampolletas>

Be Free W 3

Descripción: Suplemento alimenticio a base de alga marina y extracto de Granada, destinado a fortalecer el tejido óseo y promover el balance hormonal.

El activo principal son las algas marinas, son consideradas un superalimento, ya que entre sus principales propiedades se encuentra su riqueza en vitaminas, minerales y fibra. La gran cantidad de minerales que contienen, como el yodo, el calcio, el hierro y el fósforo, ayuda a fortalecer los huesos y los dientes.

Beneficios:

Aumenta la densidad mineral ósea

Regenera la fuerza del hueso

Reduce el riesgo de fracturas

Previene la osteoporosis

Preserva el cartílago

Regenera el tejido óseo

Reduce la inflamación

Modo de Uso: 1 stick combinado con 200 mili litros de agua, antes de dormir. **Precio:** \$600 pesos

Link de compra: <https://mireipharma.com.mx/products/w3-oe-30-sticks>

Be Free (doble-u-4) W 4

Descripción: Suplemento alimenticio a base de alga marina, extracto de yuzu y extracto de Granada, diseñado para la protección cardiovascular y balance hormonal.

El activo principal es el yuzu, un cítrico híbrido asiático que aporta una gran cantidad de vitaminas, entre las que destaca la vitamina C, la cual ayuda a producir estrógenos, provocando la reducción de algunas molestias de la menopausia.

Beneficios:

Reduce los bochornos

Previene enfermedades cardiovasculares

Promueve la humedad natural de la vagina

Aumenta la libido

Desintoxica el intestino

Modo de Uso: 1 stick combinado con 200 mili litros de agua, antes de dormir.

Precio: \$650 pesos

Link de compra: <https://mireipharma.com.mx/products/w4-sc-30-sticks>

Puntos de venta: mireipharma.com.mx, Amazon, Farmacias Especializadas, Farmacias San Isidro. Farmacias YZA, Multifarmacias, GNC y Farmacias del Ahorro.

Síntomas de la menopausia

Se pueden dividir en 3 ramas generales:

Síntomas físicos:

Bochornos: Sensación de calor súbito, generalmente en la cara, cuello y pecho, que puede durar desde unos segundos hasta varios minutos.

Sudores nocturnos: Similar a los sofocos, pero ocurre durante la noche y puede interrumpir el sueño.

Insomnio y problemas para dormir: Dificultad para conciliar o mantener el sueño.

Aumento de peso: Cambios en el metabolismo que pueden llevar al aumento de peso, especialmente en el área abdominal.

Pérdida de masa muscular y aumento de grasa corporal.

Sequedad vaginal: Disminución de la lubricación natural, lo que puede provocar molestias durante el sexo.

Dolor en las articulaciones: Dolores o rigidez en las articulaciones.

Caída del cabello y piel seca: Cambios en la textura de la piel y el cabello.

Palpitaciones: Sensación de latidos cardíacos irregulares o acelerados.

Cambios en el ciclo menstrual: Ciclos menstruales irregulares o sangrado más leve/abundante antes de la menopausia.

Sensibilidad en los senos: Dolor o hinchazón en los senos.

Dolores de cabeza o migrañas: Pueden intensificarse en algunas mujeres.

Osteoporosis: Pérdida de densidad ósea que aumenta el riesgo de fracturas.

Incontinencia urinaria: Dificultad para controlar la orina o ganas frecuentes de orinar.

Fatiga: Sensación persistente de cansancio.

Disminución de la libido: Disminución del deseo sexual.

Cambios en la apariencia de la piel: Aparición de arrugas y pérdida de elasticidad.

Síntomas emocionales y mentales:

Cambios de humor: Oscilaciones emocionales, desde tristeza hasta irritabilidad.

Ansiedad: Sentimientos de nerviosismo o inquietud.

Depresión: Sensación de tristeza persistente o desesperanza.

Problemas de concentración: Dificultad para concentrarse o recordar cosas.

Niebla mental: Sensación de estar "desconectada" o mentalmente nublada.

Pérdida de motivación: Desinterés por actividades previamente disfrutadas.

Sensación de aislamiento o soledad: Algunas mujeres sienten que están en una fase de transición en su vida, lo que puede llevar a sentimientos de soledad.

Síntomas poco comunes:

Sensación de hormigueo en las extremidades: Se puede experimentar una sensación de entumecimiento o hormigueo en las manos o pies.

Zumbidos en los oídos: También conocido como tinnitus.

Cambios en el sentido del gusto y olfato.

Sensibilidad a la temperatura: Cambios en la tolerancia al calor o al frío.

Problemas gastrointestinales: Como hinchazón, gases o indigestión.

Enfermedades cardiovasculares

Se pueden separar en tres pilares importantes:

Enfermedades del corazón:

Cardiopatía isquémica o enfermedad coronaria: Incluye la angina de pecho y el infarto de miocardio (ataque cardíaco), que ocurren por el bloqueo o estrechamiento de las arterias coronarias.

Insuficiencia cardíaca: El corazón no puede bombear suficiente sangre para satisfacer las necesidades del cuerpo, lo que provoca acumulación de líquidos y fatiga.

Arritmias: Trastornos del ritmo cardíaco, como la fibrilación auricular, taquicardia o bradicardia, que afectan la frecuencia o el ritmo de los latidos.

Miocardiopatía: Enfermedad del músculo cardíaco, que puede ser dilatada, hipertrófica, restrictiva o arritmogénica.

Enfermedad de las válvulas cardíacas: Problemas con las válvulas del corazón, como la estenosis (estrechamiento), insuficiencia (fugas) o prolusión de las válvulas.

Pericarditis: Inflamación del pericardio, la membrana que rodea el corazón.

Endocarditis: Infección de la membrana interna del corazón (endocardio), generalmente causada por bacterias.

Cardiopatía congénita: Defectos en la estructura del corazón presentes desde el nacimiento, como comunicación interventricular o defectos septales.

Enfermedades de los vasos sanguíneos:

Arteriosclerosis y aterosclerosis: Endurecimiento y estrechamiento de las arterias debido a la acumulación de placa (colesterol y otras sustancias).

Hipertensión arterial: Aumento persistente de la presión sanguínea, que puede dañar el corazón, los vasos sanguíneos y otros órganos.

Aneurisma: Dilatación anormal de un vaso sanguíneo, generalmente en la aorta, que puede romperse y causar hemorragias graves.

Enfermedad arterial periférica: Estrechamiento de las arterias en las extremidades, lo que provoca dolor y calambres, especialmente en las piernas.

Trombosis venosa profunda (TVP): Formación de un coágulo sanguíneo en una vena profunda, comúnmente en las piernas, que puede desplazarse al pulmón y causar una embolia pulmonar.

Embolia pulmonar: Bloqueo de una arteria pulmonar debido a un coágulo sanguíneo que viaja desde otra parte del cuerpo.

Venas varicosas e insuficiencia venosa crónica: Dilatación de las venas que afecta principalmente las piernas, dificultando el retorno de la sangre al corazón.

Otros trastornos cardiovasculares:

Enfermedad cerebrovascular: Incluye el accidente cerebrovascular (ictus) y el ataque isquémico transitorio, causados por el bloqueo o ruptura de los vasos que irrigan el cerebro.

Síndrome coronario agudo: Conjunto de síntomas asociados con la obstrucción súbita de una arteria coronaria, que puede llevar a un ataque cardíaco.

Hipertensión pulmonar: Presión arterial elevada en las arterias pulmonares, lo que afecta el flujo sanguíneo hacia los pulmones.

Disautonomía: Trastornos del sistema nervioso autónomo que afectan la regulación de la presión arterial y el ritmo cardíaco.

Enfermedad de Raynaud: Espasmo en las arterias pequeñas de los dedos de manos y pies, lo que provoca cambios de color, dolor y sensibilidad al frío.

Coartación de la aorta: Estrechamiento congénito de una parte de la aorta, la arteria principal del cuerpo.

¿Qué se considera sobrepeso / obesidad?

El sobrepeso es una condición en la que una persona tiene más peso del que es considerado saludable para su altura, generalmente por un exceso de grasa corporal. Puede afectar la salud, aumentando el riesgo de enfermedades como la diabetes, hipertensión y problemas cardíacos.

La obesidad es una condición de salud en la que una persona tiene un exceso de grasa corporal que puede afectar negativamente su bienestar. Es una forma más avanzada de sobrepeso y representa un riesgo mayor de enfermedades, como problemas cardíacos, diabetes tipo 2, hipertensión, y algunas formas de cáncer.

La obesidad, al igual que el sobrepeso, se mide principalmente con el Índice de Masa Corporal (IMC). La fórmula para calcular el IMC es:

IMC = peso en kg / altura en m².

Tamaños de cintura en las mujeres y lo que significan

Esto puede ser un muy buen indicador para evaluar el riesgo de enfermedades asociadas al exceso de grasa abdominal, especialmente en mujeres mayores de 35 años. La grasa que se acumula en esta zona (grasa visceral) es particularmente

peligrosa, ya que se asocia con problemas de salud como enfermedades cardiovasculares, diabetes tipo 2 e hipertensión.

Para medir la cintura correctamente, se coloca una cinta métrica alrededor del abdomen, justo arriba del ombligo, sin apretar. Aquí tienes la clasificación según las recomendaciones de la Organización Mundial de la Salud (OMS) y otras guías de salud:

Menos de 80 cm: Tamaño de cintura saludable, bajo riesgo de enfermedades metabólicas.

Entre 80 y 88 cm: Riesgo moderado. Esta medida sugiere un aumento del riesgo de problemas de salud.

Más de 88 cm: Riesgo elevado. La acumulación de grasa en esta área representa un riesgo significativo de enfermedades, especialmente cardíacas y metabólicas.

Etapas de las várices.

Las varices se desarrollan en etapas progresivas a medida que el daño en las venas aumenta. Estas etapas van desde síntomas leves hasta problemas graves en las piernas.

Etapa 0: Síntomas sin signos visibles, la persona puede sentir pesadez, dolor o cansancio en las piernas, pero sin signos visibles de varices.

Etapa 1: Arañitas, Pequeñas venas rojas, azules o moradas visibles en la piel, estas no son várices, pero si indican una pequeña insuficiencia venosa.

Etapa 2: Várices visibles, venas más grandes y visibles, que sobresalen de la piel y suelen ser de color azul o morado. Esto si viene acompañado con síntomas como dolor, hinchazón, y cansancio en las piernas.

Etapa 3: Hinchazón, o edema, aumento de la hinchazón en la zona afectada, especialmente en los tobillos y pies. Puede que la hinchazón no baje durante la noche.

Etapa 4: Cambios en la piel, y los tejidos, hiperpigmentación de las arañitas. Puede parecer un eczema venoso, con picazón, resequedad, y enrojecimiento. Se presenta también un endurecimiento de la piel y los tejidos.

Etapa 5: Úlceras venosas cicatrizadas, úlceras o heridas abiertas en la piel que se han curado, pero dejan cicatrices. Esto indica daño significativo en el sistema venoso.

Etapa 6: Úlceras venosas activas, úlceras activas, generalmente en la zona del tobillo, que son difíciles de cicatrizar son dolorosas y representan la etapa más grave de las varices.

¿Qué es la osteopenia, la osteoporosis?

La osteopenia es una condición en la que la densidad mineral ósea es más baja de lo normal, lo que significa que los huesos son más débiles y tienen un mayor riesgo de fracturas en comparación con los huesos sanos. Aunque no es tan grave como la osteoporosis, es un signo de que una persona puede estar en riesgo de desarrollar osteoporosis en el futuro.

Causas: envejecimiento, estilo de vida, condiciones médicas, medicamentos.

La osteoporosis es una enfermedad ósea caracterizada por la disminución de la densidad y la calidad del hueso, lo que aumenta el riesgo de fracturas y lesiones. Se considera una condición más grave que la osteopenia y es a menudo llamada "la enfermedad silenciosa" porque muchas personas no presentan síntomas hasta que sufren una fractura.

Causas: envejecimiento, factores hormonales, condiciones médicas, estilo de vida.

Diferencias: la osteopenia es una etapa temprana de pérdida de masa ósea que puede ser manejada con intervenciones simples, mientras que la osteoporosis es una condición más avanzada que implica un riesgo considerable de fracturas y puede requerir tratamiento médico más intensivo.

Medición de la densidad ósea

La medición de la masa ósea se realiza principalmente a través de un procedimiento llamado densitometría ósea, que evalúa la densidad mineral de los huesos. Este examen es fundamental para diagnosticar condiciones como la osteopenia y la osteoporosis.

Se recomienda que se sigan estos pasos cuando se quiera hacer la prueba:

Hay que preparar la prueba. Se recomienda que se acuda a una consulta con un doctor para ver si efectivamente se necesita de la prueba.

Hacerse la prueba. La densitometría ósea más comúnmente utilizada es la absorciometría de rayos X de energía dual (DXA o DEXA). Este método utiliza rayos X para medir la densidad mineral ósea en áreas específicas.

Te van a dar los resultados calculando el **T-score**, que compara tu densidad ósea con la de una persona joven y sana del mismo sexo.

T-score de -1.0 o superior: Normal.

T-score entre -1.0 y -2.5: Osteopenia (baja densidad ósea).

T-score de -2.5 o inferior: Osteoporosis.

La frecuencia con la que debes realizarte la densitometría ósea depende de tu edad, factores de riesgo y resultados anteriores. Generalmente, se recomienda cada 1 a 2 años para quienes tienen riesgo de osteoporosis.

3 consejos por producto para mejorar síntomas:

Be Free W1-VC:

Tip para evitar las várices: Realiza ejercicios que hagan que tus piernas se muevan, como caminar, nadar o andar en bicicleta. Ayudan a mejorar la circulación sanguínea y fortalece las venas.

Tip para tratar el ardor de piernas: Consumir alimentos ricos en antioxidantes y fibra, como frutas, verduras, granos enteros y frutos secos. Pueden ayudar a fortalecer los vasos sanguíneos y mejorar la circulación.

Tip para prevenir la pesadez en las piernas: Una vez al día eleva las piernas colocando una almohada debajo de ellas. Esto ayuda a mejorar la circulación y reducir la sensación de pesadez.

Be Free W2-MB:

Tip para cuidar tu peso después de los 35: Sal a caminar o a correr por lo menos 30 minutos al día. El ejercicio regular ayuda a mantener la masa muscular, que puede disminuir con la edad, y acelera el metabolismo.

Tip para cuidar tu alimentación: Opta por una dieta rica en frutas, verduras, proteínas magras y granos enteros. Estos alimentos te proporcionan nutrientes esenciales y te ayudan a sentirte satisfecha con menos calorías.

Tip para dormir mejor: Asegúrate de dormir entre 7 y 9 horas por noche. La falta de sueño puede afectar negativamente tu metabolismo y aumentar los antojos de alimentos poco saludables.

Be Free W3-OE:

Tip para fortalecer tus huesos: Asegúrate de incluir alimentos ricos en calcio en tu dieta diaria, como productos lácteos, vegetales de hojas verdes (col rizada, espinacas). El calcio es fundamental para la salud ósea y ayuda a mantener los huesos fuertes.

Tip para preservar el cartílago: Opta por ejercicios de bajo impacto que protejan las articulaciones mientras fortalecen los músculos alrededor de ellas. Ejercicios como nadar, andar en bicicleta y el yoga son excelentes opciones que minimizan el estrés en las articulaciones y promueven la flexibilidad.

Tip para reducir la inflamación: La hidratación adecuada es fundamental. El agua ayuda a lubricar las articulaciones y a eliminar toxinas del cuerpo. Intenta beber al menos 8 vasos de agua al día.

Be Free W4-SC:

Tip para reducir los bochornos: Algunos alimentos y bebidas pueden desencadenar bochornos, como los alimentos picantes, el café, el alcohol y los azúcares refinados. Identifica qué alimentos afectan más a tu cuerpo y trata de reducir o eliminarlos.

Tip para aumentar la libido: La comunicación abierta y honesta con tu pareja sobre tus necesidades es esencial. Esto puede ayudar a mejorar la conexión emocional y el deseo sexual.

Tip para desintoxicar tu intestino: Consumir alimentos que contienen probióticos (como yogur) y prebióticos (como plátanos).

Estos alimentos fomentan el crecimiento de bacterias intestinales saludables, que son esenciales para una buena digestión y desintoxicación.

Alimentos que evitar / limitar en la menopausia

Ajustar la dieta puede ayudar a aliviar algunos síntomas y promover una mejor salud.

Grasas saturadas y trans, pues esto puede aumentar el riesgo de enfermedades cardíacas, que es mayor en mujeres en la menopausia debido al desbalance de los niveles de estrógeno.

Evitar alimentos como: Carnes grasas como tocino, productos lácteos enteros, alimentos fritos.

Azúcares añadidos y carbohidratos refinados pueden causar picos de azúcar en la sangre, lo que aumenta el riesgo de diabetes tipo 2 y contribuye al aumento de peso.

Evitar alimentos como: Galletas, pasteles, refrescos, cereales azucarados, y pan blanco.

Alcohol puede empeorar los bochornos, y sudores nocturnos. También puede afectar la calidad del sueño y aumentar el riesgo de osteoporosis.

Evitar: vinos, cervezas, licores, y cócteles.

La cafeína puede aumentar la ansiedad, el insomnio y empeorar los bochornos. También puede contribuir a la pérdida de calcio en los huesos.

Evitar: café, té negro, refrescos con cafeína, y bebidas energéticas.

Alimentos salados y procesados pueden contribuir a la retención de líquidos y a la presión arterial alta.

Evitar: comida rápida (hamburguesas, pizza), snacks salados (papas, pretzel), y alimentos enlatados (sopas enlatadas, verduras en conserva con sal)

Alimentos que pueden ayudar si los agregas a tu dieta en la menopausia

Frutas y verduras frescas pues son ricas en antioxidantes, vitaminas, y minerales que ayudan a combatir el estrés oxidativo y a mantener la salud en general. También son bajas en calorías y altas en fibra, lo que puede ayudar a controlar el peso.

Agregar: manzanas, bayas, espinacas, brócoli, zanahorias.

Los granos enteros son ricos en fibra, lo que promueve la salud digestiva, y ayuda a mantener niveles estables de azúcar en la sangre.

Agregar: quinoa, arroz integral, avena, cebada.

Las proteínas magras son importantes para mantener la masa muscular, que tiende a disminuir con la edad. También te ayudan a sentirte satisfecha por más tiempo, y así controlar el peso.

Agregar: pollo sin piel, pavo, pescado (especialmente el salmón), legumbres (lentejas, garbanzos)

Las grasas saludables son esenciales para la salud del corazón y pueden ayudar a reducir la inflamación. También son importantes para la salud cerebral y hormonal.

Agregar: Aguacates, nueces, semillas (como chía y lino), aceite de oliva.

Lácteos bajos en grasas, pues proporcionan calcio y vitamina D, que son esenciales para la salud ósea y pueden ayudar a prevenir la osteoporosis.

Agregar: Yogur bajo en grasa, leche descremada o leche de almendras fortificada con calcio y vitamina D.

Un consumo adecuado de calcio es crucial durante la menopausia para mantener la salud ósea y prevenir la pérdida de densidad ósea.

Agregar: Verduras de hoja verde (kale, col rizada), tofu, sardinas enlatadas con espinas.

Información de la microbiota:

¿Qué es la microbiota?

los miles y millones de microorganismos (bacterias, virus, hongos) que viven dentro de nuestro cuerpo

es diversa y se encuentra en varios lugares del cuerpo, incluyendo el tracto intestinal.

Juega un papel crucial en la producción de metabolitos que impactan el equilibrio hormonal.

Su desequilibrio puede llevar a cambios en la salud

¿Qué es la disbiosis?

El desequilibrio o alteración en la microbiota, que es la comunidad de microorganismos que viven en diferentes partes del cuerpo, como el intestino, la piel y la vagina. Si estos microorganismos no están en equilibrio, puede tener efectos negativos en la salud.

¿Qué pasa cuando tu microbiota intestinal cambia?

Inflamación crónica: La disbiosis puede inducir inflamación crónica en el cuerpo. La alteración en la microbiota intestinal puede promover una inflamación sistémica de bajo grado, la cual puede afectar la salud de las venas.

Alteración del metabolismo: La disbiosis puede alterar el metabolismo de las grasas y los carbohidratos. Esto puede llevar a una mayor acumulación de grasa corporal y a problemas metabólicos como la obesidad.

Absorción de nutrientes: La salud intestinal y la composición de la microbiota afectan la absorción de nutrientes esenciales para la salud ósea, como el calcio y la vitamina D.

Alteración en el metabolismo de estrógenos: La microbiota intestinal juega un papel en el metabolismo de los estrógenos, hormonas clave para la regulación de la temperatura corporal y la función del sistema nervioso.

Impact en el estado de ánimo y la salud mental: La disbiosis puede influir en la salud mental a través del eje intestino-cerebro, afectando la producción de neurotransmisores y la regulación emocional.

Diferencias entre un Prebiótico, probiótico, y postbiótico:

Prebiótico: Alimentos que contienen fibras dietéticas que actúan como nutrientes para tu microbiota intestinal.

Beneficios:

Promueven la salud digestiva aumentando las bacterias beneficiosas.

Mejoran la regularidad intestinal y ayudan a aliviar el estreñimiento.

Contribuyen a la producción de ácidos grasos de cadena corta que tienen efectos antiinflamatorios y de soporte metabólico.

Probiótico: Son microorganismos vivos (bacterias o levaduras) que, al ser ingeridos en cantidades adecuadas, proporcionan beneficios para la salud.

Beneficios:

Mejoran la digestión y pueden ayudar a tratar o prevenir problemas gastrointestinales y el desequilibrio de la microbiota.

Apoyan la salud inmune y pueden tener efectos positivos en el estado de ánimo y la salud mental.

Postbiótico: Es un tipo de sustancia producida por bacterias buenas que ayudan a mejorar la salud intestinal y general.

Beneficios:

Mejoran la integridad de la barrera intestinal y reducen la inflamación.

Ayudan a mantener un equilibrio saludable de la microbiota y promueven la salud digestiva y metabólica.

Pueden contribuir a una respuesta inmune saludable y a una función intestinal óptima.

Be Free es un postbiótico porque:

Actúa en tu microbiota intestinal

Tiene antioxidantes que actúan en tu intestino

Metabolitos derivados de la fermentación

Propiedades antiinflamatorias

Ingredientes naturales que ayudan con la digestión

Beneficios de los ingredientes en los suplementos de Be Free:

Beneficios de la granada

Aumenta la diversidad microbiana

Mejora la circulación sanguínea

Ayuda con el control del peso

Mantiene la densidad ósea y reduce el riesgo de osteoporosis

Puede disminuir la frecuencia e intensidad de los bochornos.

Beneficios de la satsuma mandarina:

Bajo contenido en sodio y alto contenido en potasio, lo que ayuda a equilibrar los líquidos en el cuerpo.

Rica en vitamina C, ayuda a reducir el estrés oxidativo en el cuerpo, lo que a su vez, crea un ambiente más saludable.

Tiene propiedades antiinflamatorias que pueden disminuir la hinchazón y la inflamación en las piernas.

Mantiene el equilibrio electrolítico y pueden reducir el riesgo de calambres y fatiga muscular.

Produce colágeno, que fortalece los vasos sanguíneos y puede ayudar a prevenir problemas como las varices.

Beneficios del alga espirulina

Apoya el fortalecimiento muscular.

Gran fuente de hierro

Adiós a la fatiga y al cansancio

Control de peso

Control del estrés

Beneficios del alga marina:

Mantiene la densidad ósea

Ayuda a fortalecer los huesos

10 veces más calcio que la leche

Salud de los huesos y prevención de la osteoporosis

Proteína clave en la estructura y fortaleza de los huesos.

Beneficios del yuzu:

Regulación del metabolismo

Propiedades calmantes

Propiedades antioxidantes

Propiedades antinflamatorias

Refuerzo del estado de ánimo

Be Free es un postbiótico:

Es un postbiótico hecho a base de granada fermentada y otros ingredientes NATURALES que actúa sobre tu microbiota impactando el eje intestino-cerebro funcionando como un sistema que sincroniza todo el ecosistema del cuerpo.

NOSOTROS

Mirei Pharma México inició operaciones en mayo de 2018, aunque nuestra historia se remonta al año 2000 cuando la Dra. Mizhuo Nasu fundó Mirei Pharma Tokyo.

El equipo de investigación de Mirei Pharma en Japón descubrió que la microbiota intestinal modula el equilibrio hormonal de la mujer, activando los estrógenos.

MIREI PHARMA comenzó con el descubrimiento de que las mujeres sanas tienen una salud intestinal óptima que afecta el equilibrio hormonal. Este descubrimiento ofrece una solución para transformar la salud de las mujeres y apoyarlas en cada etapa.

Nuestra filosofía está representada por el logotipo, que refleja la transformación en mariposa de una mujer que continúa renovándose constantemente.

Somos la fuerza de la innovación para transformar la salud.

ORIGEN

La longevidad de la mujer japonesa

En la isla de Okinawa se encuentran las mujeres con la longevidad más alta del mundo.

Durante más de 20 años, la Dra. Mizuho Nasu estudió el porqué y descubrió que su gran salud se debe a la nutrición basada en diversos alimentos fermentados, especialmente la granada, lo que les ha permitido desarrollar una microbiota óptima para el equilibrio hormonal.

BENEFICIOS

Granada, la mejor aliada para el bienestar hormonal

La Dra. Mizuho Nasu analizó la granada, que es la base de la salud de las mujeres en Okinawa, y descubrió que los probióticos que crecen en la flor de esta fruta son los responsables del bienestar de estas mujeres. Además, es la responsable de su piel sana, su gran vitalidad y corazón saludable.

Entre las propiedades de este antioxidante natural, podemos decir que ayuda a modular los receptores de estrógeno, disminuir la grasa corporal, reducir el colesterol y la presión arterial, prevenir la osteoporosis y ser fuente de urolitinas, que son fuente de la microbiota del colon.

MICROBIOTA

El papel de la microbiota intestinal en la menopausia.

La microbiota es un conjunto de microorganismos que habitan en nuestros intestinos y que están relacionados con la salud de las mujeres, ya que afectan el equilibrio hormonal. Es por esta razón que los organismos beneficiosos, llamados probióticos, pueden contribuir a un mayor bienestar en la etapa de la menopausia.

Nuestra tecnología se basa en comprender el lenguaje de estas bacterias probióticas, ya que se comunican con las células humanas mediante la secreción de metabolitos. La señal enviada por los metabolitos promueve el equilibrio de la microbiota y la buena salud.

TECNOLOGÍA

COLD-BIO FUSION es nuestra tecnología de biofermentación capaz de regular la microbiota intestinal e influir en el metabolismo del cuerpo para regenerar sus células y ayudar a prevenir algunas enfermedades.

El extracto de granada fermentada ayuda a equilibrar los metabolitos naturales del cuerpo y

a regula la producción de estrógenos, además contribuye a crear una barrera intestinal y fortalecer el sistema inmunitario.

Respuestas de las FAQs (Preguntas frecuentes) en nuestra página

¿Cuáles Son Las Opciones De Envío Disponibles Y Sus Costos?

Al hacer la compra a través de nuestra tienda en línea, se hace el envío a través de ESTAFETA y el envío a toda la república es gratis.

¿Cuánto Tiempo Se Tarda En Enviar Y Recibir Un Pedido?

El envío tarda en llegar a tu domicilio de 3 a 5 días hábiles.

¿Ofrecen Envío Internacional?

Por el momento no hacemos envíos internacionales.

¿Cuáles Son Las Opciones De Seguimiento De Envío Disponibles?

Se manda el estatus del envío al correo electrónico proporcionado al hacer su pedido.

¿Puedo Modificar La Dirección De Envío Después De Realizar Un Pedido?

No, después de hacer tu pedido, no se puede modificar tu dirección.

¿Qué Sucede Si Mi Pedido Se Extravió O Llega Dañado?

Manda un correo a befree@mireipharma.com para que se haga un reporte y podamos darle seguimiento a tu pedido.

¿Ofrecen Envío Exprés Para Entregas Más Rápidas?

No ofrecemos envío exprés.

¿Cuál Es La Política De Devolución En Caso De Problemas Con La Entrega?

No contamos con devoluciones. Se tendría que hacer un reporte al correo:

befree@mireipharma.com para poder darle seguimiento.

¿Cuanto dura el producto? / ¿Cuanto duran los suplementos alimenticios de Be Free?

Cada suplemento está diseñado para un suministro de 30 días. Además, ofrecemos un kit que incluye los cuatro productos, el cual está diseñado para durar 20 días.

¿Se pueden consumir todos los suplementos alimenticios de Be Free juntos?

Sí, los suplementos alimenticios de Be Free se pueden consumir juntos o por separado, dependiendo de los síntomas y las necesidades individuales de cada persona.

¿Se pueden consumir los suplementos alimenticios de Be Free con otros medicamentos o productos?

Sí, los suplementos de Be Free se pueden consumir junto con otros medicamentos o productos sin ningún problema. Sin embargo, siempre es recomendable consultar a un profesional de la salud antes de hacerlo.

¿A partir de qué edad se puede consumir el producto?

Es recomendable para mujeres adultas, mayores de 40 años.

Redes Sociales de la Empresa:

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Instagram: <https://www.instagram.com/mx.befree/>

TikTok: <https://www.tiktok.com/@befreemx>

YouTube: <https://www.youtube.com/@BeFreeMexico>

Invita a los usuarios a seguir a la empresa en:

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TikTok como @befreemx

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{Ante preguntas como las siguientes responde el precio del producto y los puntos de venta:}

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¿Cómo lo puedo comprar?

¿Dónde lo puedo adquirir?

¿Dónde puedo adquirirlo?

¿Dónde se compra?

¿Dónde lo consigo?

¿Cómo lo consigo?

¿Cómo puedo obtenerlo?

¿Cómo lo puedo conseguir?

¿Cómo puedo conseguirlo?

Lo quiero comprar

Quiero comprarlo

Quiero comprar

Quiero adquirirlo

Quisiera hacer una compra ¿En dónde lo venden?

¿En dónde se consigue? ¿En dónde se compra? ¿Dónde puedo encontrarlo? ¿Dónde lo puedo pedir? ¿Dónde puedo pedirlo? ¿Dónde lo venden?

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Influence of Oral and Gut Microbiota in the Health of Menopausal Women

Angélica T. Vieira¹, Paula M. Castelo^{2,3}, Daniel A. Ribeiro^{3,4} and Caroline M. Ferreira^{2,3*}

¹ Department of Biochemistry and Immunology, Institute of Biological Sciences, Federal University of Minas Gerais, Belo Horizonte, Brazil, ² Department of Pharmaceutics Sciences, Institute of Environmental, Chemical and Pharmaceutical Sciences, Universidade Federal de São Paulo, Diadema, Brazil, ³ Pathology Graduate Program, Universidade Federal de São Paulo, São Paulo, Brazil, ⁴ Department of Biosciences, Universidade Federal de São Paulo, Santos, Brazil

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United States

*Correspondence:

Caroline M. Ferreira
caroline.nu.ferreira@gmail.com

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Sex differences in gut microbiota are acknowledged, and evidence suggests that gut microbiota may have a role in higher incidence and/or severity of autoimmune diseases in females. Additionally, it has been suggested that oral, vaginal, and gut microbiota composition can be regulated by estrogen levels. The association of vaginal microbiota with vulvovaginal atrophy at menopause is well described in the literature. However, the relevance of oral and gut microbiota modulation in the immune system during estrogen deficiency and its effect on inflammatory diseases is not well explored. Estrogen deficiency is a condition that occurs in menopausal women, and it can last approximately 30 years of a woman's life. The purpose of this mini-review is to highlight the importance of alterations in the oral and gut microbiota during estrogen deficiency and their effect on oral and inflammatory diseases that are associated with menopause. Considering that hormone replacement therapy is not always recommended or sufficient to prevent or treat menopause-related disease, we will also discuss the use of probiotics and prebiotics as an option for the prevention or treatment of these diseases.

Keywords: saliva, oral health, mouth diseases, gut microbiota, estrogen, menopause

INTRODUCTION

We harbor trillions of microorganisms that associate with specific tissues and are termed microbiota. This rich community of microorganisms, mostly bacteria, has co-evolved in a symbiotic relationship with humans in such a way that it is now essential for several physiological functions and controls many aspects of host physiology (Backhed et al., 2005; Backhed, 2012; Grover and Kashyap, 2014).

One of the factors that plays a pivotal role in microbiota modulation, although broadly understudied in current research, is the change in female sexual hormones throughout life. Two phases occur in a woman's life that are characterized by several physiological, metabolic and immunological changes: menarche, or the first menstruation of a woman, which occurs during adolescence between 10 and 15 years of age (Hoffmann et al., 2004), and menopause, which occurs between age 45 and 55 and includes the cessation of menstrual periods and loss of the reproductive function of the ovaries (Brotman et al., 2014). In fact, estrogen and the microbiota of a woman's body tend to be investigated more extensively during the woman's reproductive years than during menopause or the phase of estrogen decline. One exception is the vaginal microbiota,

which has been widely investigated during menopause. Here, we consider menopause or the menopausal phase, including perimenopause (before menopause), menopause and postmenopause (after menopause).

Considering that menopause can last for approximately 30 years of a woman's life (Brotman et al., 2014), the purpose of this mini-review is to highlight the importance of alterations in the oral and gut microbiota during estrogen deficiency and determine their relevance in oral infections and inflammatory diseases that are associated with menopause.

THE INTERACTION BETWEEN ORAL MICROBIOTA AND FEMALE SEX HORMONES

The oral cavity (mouth) is composed of several distinct microbial habitats, including the lips, the teeth, the gingival sulcus, the tongue, the cheeks, the palate and the tonsils, which are colonized by hundreds of different bacterial, viral, and fungal species (Dewhirst et al., 2010; Yost et al., 2015). The microbial communities associated with these structures are in symbiosis with the host (Sanz et al., 2017). However, in the presence of stressors that can perturb this homeostasis, several oral infectious diseases may appear, including dental caries and periodontitis (Almstahl et al., 2010; Dewhirst et al., 2010). Many of these disease are recognized to be caused by the consortia of organisms in a biofilm rather than a single pathogen (Jenkinson and Lamont, 2005). In addition, poor oral health and oral diseases may be associated with many systemic diseases (Seymour et al., 2007), such as cardiovascular diseases (Joshipura et al., 1996; Monteburgnoli et al., 2004; Belenguer et al., 2006), stroke (Joshipura et al., 2003), preterm birth (Offenbacher et al., 1998), diabetes (Genco et al., 2005), and pneumonia (Awano et al., 2008).

In healthy individuals, the microorganisms found in the mouth with the largest representation include *Streptococcus*, *Actinomyces*, *Veillonella*, *Fusobacterium*, *Porphyromonas*, *Prevotella*, *Treponema*, *Neisseria*, *Haemophilus*, *Eubacteria*, *Lactobacterium*, *Capnocytophaga*, *Eikenella*, *Leptotrichia*, *Peptostreptococcus*, *Staphylococcus*, and *Propionibacterium* (Jenkinson and Lamont, 2005; Liu et al., 2012). The behavior of these organisms can be very dynamic and adapt to a wide range of environments and interactions with other microbial species while aggregated in biofilms over the oral surfaces.

Estrogen receptor-beta has been detected in the oral mucosa and salivary glands (Valimaa et al., 2004), and some evidence shows age-related hormonal changes in the exfoliated normal buccal mucosa of women (Donald et al., 2013). Moreover, the vaginal and buccal epithelia share some microscopic similarities. As observed by Thompson et al. (2001), the patterns of surface keratinization and the distribution and appearance of the lipid lamellae in the intercellular spaces were similar between vaginal and buccal epithelial samples of postmenopausal women. Therefore, given that many menopausal women also suffer from oral discomforts in addition to climacteric symptoms (Meurman et al., 2009), an understanding of the impact of female sex

hormones on the characteristics of the oral microbiota may be clinically relevant, especially during menopause. Some of the main complaints from women in menopause include dry mouth and tooth loss, and the existing data have focused on the salivary microbial composition and the microbiota characteristics of the gingival sulcus. Therefore, this review will explore the main findings of the relationship between the oral microbiota and menopause in saliva and periodontal support.

Saliva

Saliva plays an important role in the maintenance of oral health integrity and the protection against dental caries and other oral diseases (Marsh et al., 2016; Wang et al., 2016). The salivary microbiota is highly diverse and complex (Curtis et al., 2011).

Estrogen and menopause-related hormonal imbalances are believed to affect oral health (Cao et al., 2007). According to the literature (Meurman et al., 2009), together with climacteric complaints, various oral discomforts are reported in menopausal women. The main peri- and postmenopausal symptoms include xerostomia (subjective oral dryness) and/or hyposalivation (Mahesh et al., 2014), which may increase the occurrence of mucosal and dental diseases, such as candidiasis. Few studies have investigated the effects of hormone replacement therapy in such patients (Mahesh et al., 2014; Lago et al., 2015), although the existing results show an improvement in symptoms following such treatment (Mahesh et al., 2014; Lago et al., 2015).

The quantitative and qualitative changes in saliva may alter the regular homeostasis of oral health, subsequently leading to specific changes in the salivary bacterial composition (Nasidze et al., 2009, 2011; Belstrøm et al., 2014). However, recent findings have shown that patients with severe hyposalivation do not differ in their bacterial profiles compared with those with normal salivary flow rates (Belstrom et al., 2016), although the corresponding study did not focus on the evaluation of such differences between menopausal and non-menopausal women.

Because the salivary composition may be influenced by the presence of oral diseases, prescribed medications and general health (Belstrom et al., 2016), researchers must pay attention to the sample size and control for confounding factors when revising the existing literature to confirm the external validity of any quantitative and qualitative changes in saliva related to menopause.

Periodontal Support

The periodontium is the specialized tissue that both surrounds and supports the teeth. Periodontal disease, which includes gingivitis and periodontitis, is highly prevalent in adults, and disease severity increases with age. This inflammatory disease develops over time with the accumulation of biofilm (dental plaque), bacterial dysbiosis, the formation of periodontal pockets, gum recession, and tissue destruction (including alveolar bone loss), which can ultimately lead to tooth loss (Michaud et al., 2017).

Fluctuating female sexual hormone levels in menopausal women may represent key factors that respond to changes detected in the oral cavity (Dutt et al., 2013). Menopause is accompanied by decreased bone density, which may have

implications for oral health such as the risk of enhanced progression of periodontal infections and tooth loss (Hernandez-Viguera et al., 2016). According to the literature, sex-related hormonal changes may cause the gums to become more susceptible to plaque and create a much higher risk for gingivitis and advanced periodontitis (Suresh and Radfar, 2004).

Periodontitis is a chronic inflammatory process that occurs in response to an increase in Gram-negative bacteria in the biofilm (Ruby and Barbeau, 2002), affecting the tissues that surround and support the teeth. Specific bacterial species, such as *Porphyromonas gingivalis* and *Tannerella forsythensis*, were found to be important in the etiology of periodontitis in postmenopausal women (Brennan et al., 2007). In addition, changes in periodontal status were found to be associated with variations in sex hormone levels (Mascarenhas et al., 2003), and the occurrence of periodontitis was reported to be greater in postmenopausal women who did not receive hormone replacement than in premenopausal women (Haas et al., 2009). Therefore, from a clinical point of view, the roles of sex hormones and hormone therapy in the prevalence of subgingival bacterial infection in peri- and postmenopausal women are of great interest.

In a cohort study that included 106 women aged 50–58 years, hormone replacement therapy led to a decreased number of positive samples showing the periodontal pathogens *P. gingivalis*, *Prevotella intermedia*, and *T. forsythia* from the subgingival plaque (Tarkkila et al., 2010). Consistent with this result, a previous study found improved periodontal probing depths and tooth mobility in 190 randomized women who received hormone therapy for 1 year (López-Marcos et al., 2005). Conversely, Pilgram et al. (2002) investigated 135 women in a randomized, controlled trial who received estrogen replacement for 3 years and did not find any changes in clinical parameters such as the attachment of teeth or the bone mineral density of the lumbar spine. In mice, estrogen seems to modulate IL-1 production and participate in the resistance of females to disseminating dentoalveolar infections, leading to the enhanced localization of these infections (Youssef and Stashenko, 2017), which draws attention to the potential role of sex-related hormones in the modulation of oral mucosal infections.

Non-conventional treatment approaches for oral infections, with a particular emphasis on dental biofilm-related diseases, have gained attention in recent years. The use of probiotics and prebiotics to improve gastrointestinal health has now led to an interest in using these treatments to control oral diseases (Allaker and Ian Douglas, 2015). However, few studies have focused on recovery of the oral equilibrium by promoting beneficial microbiota. Despite differences in the composition of the gut and oral microbiota, the community types observed in the gut are predictive of the community observed in the mouth and vice versa (Ding and Schloss, 2014). Among other host factors, the oral microbiota serves as an inoculum for the intestine, and the microorganisms that find adequate conditions in the mouth give rise to distinct types of communities in the intestine. Interestingly, oral inoculation with *P. gingivalis* in experimental models leads to a change in the intestinal microbiota, which is a possible mechanism for the establishment

of diseases associated with periodontitis, such as cardiovascular diseases (Arimatsu et al., 2014). In this sense, understanding the role of health-associated microorganisms may have utility in the application of these approaches for the prevention and treatment of disease (Sanz et al., 2017).

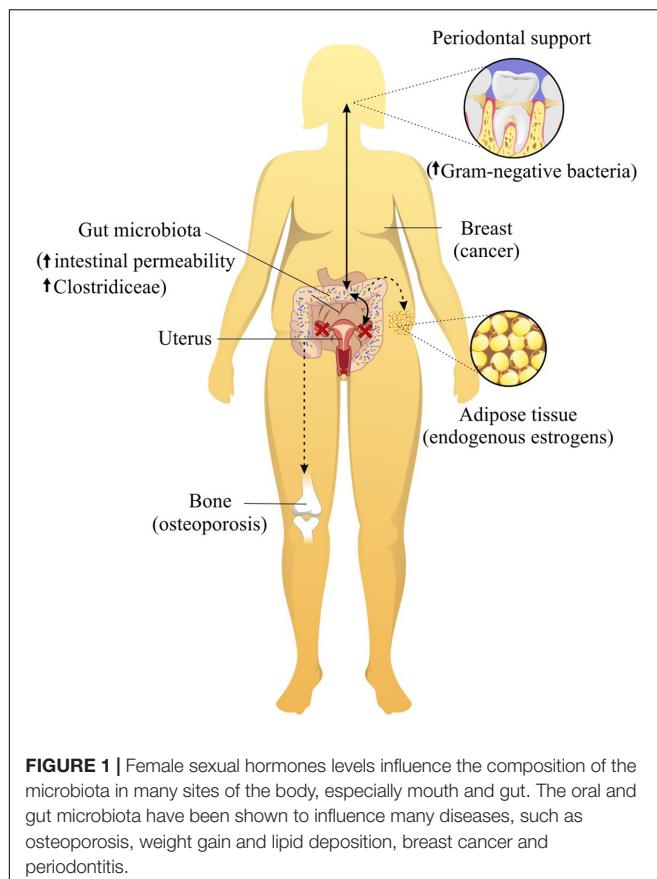
THE INTERACTION BETWEEN GUT MICROBIOTA AND FEMALE SEX HORMONES

As mentioned earlier, female sex hormones levels influence the composition of the microbiota in many sites of the body, especially the gut. Due to intimate contact with the larger gut immune system, the gut microbiota has been shown to influence many diseases outside of this organ (Figure 1). Accordingly, imbalance of the gut microbiota, called dysbiosis, has been extensively related to metabolic and immunological diseases. Interestingly, the presence or absence of estrogen may be able to alter the gut microbiota equilibrium and corresponding disease pathways. Some autoimmune diseases affect more often women than men, including systemic lupus erythematosus (Jiang et al., 2005), Sjogren's syndrome (Patel and Shahane, 2014) and rheumatoid arthritis (Oliver and Silman, 2009). Gender differences have also been reported for the outcome of microbial infections (Fischer et al., 2015). Interestingly, the onset of autoimmune diseases, asthma (Akinbami et al., 2016) and other diseases occurs after menarche or during the reproductive period of women. Experimental findings in mice have shown that the interactions among the microbiota, female sexual hormones, and immunity are associated with the development of autoimmune diseases (Yurkovetskiy et al., 2013, 2015), including type 1 diabetes (Markle et al., 2013) and rheumatoid arthritis (Wu et al., 2010). The non-obese diabetic (NOD) mouse exhibits spontaneous, immune-mediated pancreatic beta cell destruction causing type 1 diabetes (T1D) with a complex genetic and environmental etiology. The NOD T1D incidence shows a strong 2:1 female to male sex bias (Markle et al., 2013). Interestingly, germ-free NOD female mice lack this gender bias for diabetes. Additionally, after castration, males exhibit a similar microbiota composition and T1D incidence to females (Markle et al., 2013). In general, this study shows that the microbiome is a causal factor and not simply a consequence of autoimmune disease.

The Relevance of the Gut Microbiota in the Health of Menopausal Women

When the interaction between the gut microbiota and estrogen is altered due to a lack of estrogen, this relationship is restructured according to the new circumstances. However, host functional alterations, such as metabolic and immunological changes, also occur.

Obesity affects 65% of postmenopausal women and is associated with the onset of metabolic dysfunction (Leenens et al., 2017). Multiple studies have suggested that postmenopausal women exhibit increased total fat mass and abdominal fat and



decreased lean body mass compared with those of premenopausal women, regardless of aging (Aloia et al., 1995; Schreiner et al., 1996; Cordina-Duverger et al., 2016). The accumulation of abdominal fat in postmenopausal women appears to be a critical factor in the development of insulin resistance and type 2 diabetes (Lobo et al., 2014), and the relationship between the gut microbiota and a lack of estrogen is likely responsible for weight gain and lipid deposition during menopause (Figure 1). The gut microbiota can metabolize estrogen-like compounds such as isoflavonoids, which are found in soy foods, and promote the growth of some specific bacteria (Frankenfeld et al., 2014; Chen and Madak-Erdogan, 2016; Miller et al., 2017). Indeed, the administration of soy isoflavones to postmenopausal women was shown to increase the concentration of *Bifidobacterium* and suppress Clostridiaceae, which are known to be involved in inflammatory diseases (Frankenfeld et al., 2014; Nakatsu et al., 2014). This suppression of Clostridiaceae, a family of Clostridia associated with obesity (Figure 1), likely explains why diets containing phytoestrogens have been shown to improve weight gain in menopausal women.

Few studies have investigated whether prebiotics and probiotics can improve insulin sensitivity in postmenopausal women or body fat in mice. The intake of flaxseed mucilage, a prebiotic, is known to improve insulin sensitivity and alter the gut microbiota in obese postmenopausal women (Brahe et al., 2015). Thus far, the implications of the gut microbiota with low

levels or the absence of estrogen hormone in the metabolism of women have not been sufficiently studied and require further clarification.

Another link between the gut microbiome and menopausal health is related to bone. Interesting, the gut microbiota has also been found to influence bone homeostasis. Approximately one in two women over age 50 will break a bone because of osteoporosis. A study that involved twenty postmenopausal women with a mean age of 65 years showed that the group that consumed *Lactobacillus helveticus*-fermented milk had increased serum calcium levels and reduced bone reabsorption compared with those of the control milk consumption group (Narva et al., 2004). Experimental studies have also demonstrated similar results. For instance, *L. reuteri* treatment significantly protected ovariectomized mice from bone loss and increases in bone marrow CD4+ T-lymphocytes, which promote osteoclastogenesis (Britton et al., 2014). Another study that investigated probiotic treatment for cortical bone loss found reduced expression of two inflammatory cytokines, TNF- α and IL-1 β , and increased expression of osteoprotegerin, a potent inhibitor of osteoclastogenesis, in the cortical bone of ovariectomized mice (Ohlsson et al., 2014). Additionally, sex steroid deprivation has been reported to promote intestinal permeability (Figure 1), and the oral administration of *L. rhamnosus* GG (LGG) or VSL#3 (a combination of tree probiotics) to estrogen-deficient mice significantly reinforced intestinal barrier integrity and completely protected the mice against sex steroid depletion-induced bone loss (Li et al., 2016). Importantly, to confirm the role of the gut microbiota in bone health, another experiment also showed that germ-free mice are protected against the bone loss induced by the absence of sex steroids (Li et al., 2016).

We must mention that the gut microbiota may influence the risk for breast cancer through effects on endogenous estrogens produced by adipose tissue in postmenopausal women (Figure 1) (Key et al., 2003). A cross-sectional study on 60 healthy postmenopausal women found that women with a more diverse gut microbiome and an abundance of four Clostridia taxa exhibited an elevated urinary ratio of hydroxylated estrogen metabolites to parent estrogens (Fuhrman et al., 2014), which is related to the etiology of breast cancer (Flores et al., 2012; Kwa et al., 2016). However, another study compared 48 postmenopausal breast cancer patients and 48 control patients and observed that postmenopausal women with breast cancer exhibited an altered composition and estrogen-independent low diversity of their microbiota (Goedert et al., 2015). These different findings on gut microbiota diversity and breast cancer could be explained by the fact that disease outcome or disease stage can also affect the microbiota. In this scenario, the consumption of the soy isoflavone daidzein, which is metabolized by some bacteria of the microbiota to generate equol and O-desmethylangolensin (ODMA), could represent a therapeutic strategy for breast cancer prevention. Some, but not all, studies have shown a lower risk of breast cancer associated with equol production (Hullar et al., 2014). However, only approximately 30–50% of the population can metabolize daidzein (Frankenfeld et al., 2004; Uehara, 2013; Nakatsu et al., 2014) to equol, likely

due to the host microbiota. Therefore, an investigation into the administration of the soy isoflavone daidzein together with probiotic bacteria to produce equol is warranted and could offer benefits in the prevention of breast cancer in menopausal women.

CONCLUDING REMARKS

Many chronic diseases can emerge after estrogen levels decline, which will affect a considerable part of a woman's life. Understanding the role of the microbiota in women's health at the menopausal phase could help to improve strategies for microbiota modulation and prevent dysfunction. The oral and gut microbiotas have been extensively studied in women of reproductive age, while the menopausal period has been somewhat overlooked. The use of hormone replacement is not indicated for all menopausal women, and considering that probiotics and prebiotics can affect the dysfunction of bone, adipose tissue, oral and other tissues, such treatments may constitute an important therapeutic strategy. Pro- and prebiotics can also be used in conjunction

with menopause hormone therapy and may attenuate the side effects that can arise from hormone replacement. In conclusion, the scientific findings published to date do not definitively demonstrate how non-vaginal microbiota sites influence the health of menopausal women. Thus, many questions remain unanswered and warrant further investigation to improve the quality of life of menopausal women.

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AV, PC, DR, and CF drafted and revised the manuscript.

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Urolithins: The Colon Microbiota Metabolites as Endocrine Modulators: Prospects and Perspectives

Ravindran Vini¹, Juberiya M. Azeez¹, Viji Remadevi¹, T. R. Susmi¹, R. S. Ayswarya¹, Anjana Sasikumar Sujatha¹, Parvathy Muraleedharan², Lakshmi Mohan Lathika¹ and Sreeja Sreeharshan^{1*}

¹ Cancer Biology Division, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, India, ² Botany Department, Mount Carmel College, Bengaluru, India

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Michele Barone,
University of Bari Aldo Moro, Italy

Reviewed by:

Antonio González-Sarriás,
Center for Edaphology and Applied
Biology of Segura, Spanish National
Research Council (CSIC), Spain
Kate J. Claycombe,
United States Department of
Agriculture (USDA), United States

***Correspondence:**

Sreeja Sreeharshan
ssreeja@rgcb.res.in

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Selective estrogen receptor modulators (SERMs) have been used in hormone related disorders, and their role in clinical medicine is evolving. Tamoxifen and raloxifen are the most commonly used synthetic SERMs, and their long-term use are known to create side effects. Hence, efforts have been directed to identify molecules which could retain the beneficial effects of estrogen, at the same time produce minimal side effects. Urolithins, the products of colon microbiota from ellagitannin rich foodstuff, have immense health benefits and have been demonstrated to bind to estrogen receptors. This class of compounds holds promise as therapeutic and nutritional supplement in cardiovascular disorders, osteoporosis, muscle health, neurological disorders, and cancers of breast, endometrium, and prostate, or, in essence, most of the hormone/endocrine-dependent diseases. One of our findings from the past decade of research on SERMs and estrogen modulators, showed that pomegranate, one of the indirect but major sources of urolithins, can act as SERM. The prospect of urolithins to act as agonist, antagonist, or SERM will depend on its structure; the estrogen receptor conformational change, availability and abundance of co-activators/co-repressors in the target tissues, and also the presence of other estrogen receptor ligands. Given that, urolithins need to be carefully studied for its SERM activity considering the pleotropic action of estrogen receptors and its numerous roles in physiological systems. In this review, we unveil the possibility of urolithins as a potent SERM, which we are currently investigating, in the hormone dependent tissues.

Keywords: urolithin, estrogen receptor, selective estrogen receptor modulators, pomegranate (*Punica granatum* L.), PhytoSERM

INTRODUCTION

Selective estrogen receptor modulators (SERMs) are non-steroidal compounds that bind to estrogen receptors and can act like estrogen or be a partial agonist or antagonist with mixed activity depending on the tissue it acts. Tamoxifen and raloxifen are the most commonly used SERMs in treating breast cancer, which is often observed to exert side effects in hormone dependent-tissues.

Tamoxifen, for instance, though osteoprotective like estrogen (1, 2), is reported to increase the uterine weight, endometrial cancer, stroke, and pulmonary embolism (3). A drug that has protective effects in estrogen-dependent tissues and prevents its deleterious effects would serve as an ideal SERM (4). Overcoming the side effects of synthetic SERMs is highly coveted for treating ER-positive breast cancer and other hormone related disorders. Hence, there has been an extensive search for alternatives from plant-based molecules with structural and functional resemblance to estrogens such as phytoestrogens. These are present in soy, grains, vegetables, and berries and are often metabolized by microbiota to form compounds, with or without having an estrogen-like activity (5). Many times, these phytoestrogens are metabolized by gut microbiota, which often have a stronger activity attributed to their higher lipophilicity, leading to a better absorption, and a higher affinity with estrogen receptors (6). These metabolites can, in turn, modulate the gut microbiota rendering a bidirectional relationship (7, 8). For instance, S-equol derived from daidzein by an intestinal bacterial metabolism also displays a profile like that of the daidzein's, and is of clinical importance (6, 9). Notably, many of the phytoestrogens like genistein, coumestrol, and liquiritigenin display more affinity toward estrogen receptor β (ER β) than to estrogen receptor α (ER α), but the implications and underpinnings of these differences remain elusive (10). It is probable that those tissues where ER β is critical, such as ovary, prostate, lung, cardiovascular, and central nervous systems (CNSs) (11), might be more influenced by these compounds.

Pomegranate has been known to have extensive medicinal properties which have been attributed to its constituents, working individually or in combination (12, 13). We have also demonstrated that pomegranate can act as SERM (4). Pomegranate is rich in ellagitannins and ellagic acid, which is further metabolized to urolithins by a specific colon microbiota. Ellagitannins and ellagic acid are also found in certain berries and nuts like walnuts and pecans. However, there is lot of inter-individual variability in the presence and abundance of ellagic acid and urolithins in plasma, urine, and feces of the individuals consuming ellagitannin-rich food, which could be primarily due to the presence, absence, or abundance of some specific microbiota (14). Urolithin family, characterized by a chemical structure containing α -benzo-coumarin scaffold, majorly include Urolithin A (UA), Urolithin B (UB), Urolithin C (UC), Iso-Urolithin A (Iso-UA), the recently discovered Urolithin M7R, Urolithin CR, and Urolithin AR (15). The main metabolites found in plasma, tissues, and excreted in urine and feces include UA, UB, and Iso-UA, which are subsequently absorbed and metabolized into their corresponding phase II conjugates (glucuronides or sulfates) and can persist in the bloodstream up to 3–4 days after the intake (13). Urolithins are understood to be actively glucuronidated in the large intestinal enterocytes before entering the bloodstream. Their maximal concentrations in the plasma can reach up to 35 μ M for glucuronide and 8-O-glucuronide, 0.745 μ M for Iso-UA 3-O-glucuronide, and 7.3 μ M for and urolithin B 3-O-glucuronide (16). Repeated consumption of ellagitannin-containing food products can

significantly increase the concentration of these conjugates in urine (16). Among the urolithins, UA and its conjugates are found at the highest concentrations in human plasma ranging from 0.024 to 35 μ M. Urolithins are detected in high concentrations in the colon and can also reach the systemic tissues such as the prostate and mammary gland (13). Direct supplementation with UA significantly increases plasma levels and provides more than six-fold exposure to UA vs. pomegranate juice (17).

Accumulating evidence suggests urolithins have extensive health benefits (18). It has been shown that urolithins have estrogenic and antiestrogenic activity (19) via competitive binding assays, proliferation assays (20), and transactivation assays (21), and is predicted to bind to ER α in a similar orientation as that of the estrogen (21). However, the conjugates of urolithins, which reach the breast tissue after the ellagitannin intake, apparently lack estrogenic and anti-estrogenic activity (22). The ellagic acid from which urolithins are derived have also been reported to exhibit estrogenic activity at low concentrations (10^{-7} to 10^{-9} M), via ER α , whereas it was a complete estrogen antagonist via ER β (23), though another investigation demonstrates absence of any estrogenicity or antiestrogenic activity in ellagic acid (21). Notably, UA and UB have been known to inhibit aromatase (24) and 17 β -hydroxysteroid dehydrogenases (25), which are the enzymes critical for estradiol synthesis. All these pointedly illustrate the ability of urolithins to have estrogenic/anti-estrogenic or SERM-like profile. Briefly, estrogenic chemicals are those that can directly activate or inhibit estrogen action or can indirectly modulate its action. These can act as endocrine disruptors, which are defined as “an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes” (26). The SERMs are cornerstone strategy to treat breast cancers, infertility problems, postmenopausal problems like hot flashes, osteoporosis, and for hormone replacement therapy. Hence, this implies that it is highly beneficial if urolithins can be employed as SERMs or as estrogenic compounds, with minimum side effects. Of note, urolithins are considered safe according to toxicity studies (27, 28), and, most importantly, UA has been recently recognized by food drug administration (FDA, USA) as GRAS (Generally Recognized As Safe) for its use as an ingredient. In this review, we explore the prospect of urolithins to act as endocrine modulators/disruptors by consolidating and connecting the existing body of evidence that underpins the health benefits of urolithins in hormone-dependent tissues and propose that it can act as an estrogen agonist, or antagonist or as SERMs, and detail its potential to modulate the hormone related pathways. The following sections unfold the benefits of urolithins in tissues where estrogen has a remarkable role. This includes its anti-inflammatory potential, cardiovascular benefits, breast, endometrial and prostate cancer protection, bone, muscle, and cognitive health where estrogen receptors are abundant and play a pivotal role.

COLON BACTERIA: THE COOKS WHO BROUGHT OUT THE DELICACY

Right from the mode of delivery to the kind of feeding pattern, the environment and the dietary pattern mold the gut microbiota. The response to diet depends on the type of bacteria that inhabits the gut and also interaction of the host microbe. This process is cyclic and inter-dependent (29). Similarly, the nutritional availability and, hence, therapeutic, or preventive effect of a diet can vary with microbiome features and their abundance. The inter-individual variability in the presence and abundance of ellagitannins/urolithins in plasma and urine samples after consumption of ellagitannin rich food was suggestive of their microbial origin in colon. Speculations were put to rest when results from Cerdà et al. (30) confirmed that urolithins and its types correlated with the type of the fecal bacteria. This affirmed the microbial origin of urolithins in humans and explains the difference in the therapeutic and nutritional effects of pomegranate and berries that have similar rich composition of ellagitannins. This discovery led to the active research in identification of the microorganisms which can convert ellagitannins/ellagic acid to different types of urolithins. Selma et al. identified intestinal bacterial species from human feces, namely, *Gordonibacter urolithinfaciens* and *Gordonibacter pamelaiae* (31), belonging to the family Eggerthellaceae, which transformed the ellagic acid into UC, and another strain CEBAS 4A4, belonging to a new genus from the same family, could produce Iso-UA (32) under anaerobic condition leading to the categorizing of individuals into three metabotypes, according to the gut microbiota composition (33). After ingestion of ellagitannin-rich food products, individuals without urolithins production belonged to metabotype 0, with UA production as the unique final product that fits into metabotype A, and UB and/or Iso-UA belongs to metabotype B (14, 18). Thus, this difference in microbiota composition would further influence the health benefits associated with ellagitannin-rich food (34). Notably, urolithins have been found in breast milk of mothers, who consume ellagitannin rich walnut, and it resembles Urolithin metabotypes of the mothers as well (35). Investigations on how these bacteria can improve the metabolism of an ellagitannin-rich food, how would it further bring about health benefits, and an examination of its safety aspects are vital before considering them as a potential probiotic.

ANTI-INFLAMMATORY ACTIVITY AND CARDIOVASCULAR PROTECTION

Ellagitannins and urolithins have antioxidant (36), anti-inflammatory (37–41), and immunomodulatory properties (42). Urolithins inhibit NF- κ b in colon fibroblast (43), in osteoarthritic models (44), and in rat primary chondrocytes (45), but whether they act via estrogen receptors or membrane receptors like estrogen do, is not studied estrogens (46) is not studied. The UA and its metabolites have been shown to be protective in cardiac health (47, 48). *In vivo* studies with streptozotocin-induced type-1 diabetes rats demonstrated

that urolithins administration reduced the myocardial expression of the pro-inflammatory cytokine fractalkine, thus, improving the cardiac performance (49). Furthermore, urolithin B-glucuronide (UB-glu) could counteract trimethylamine-N-oxide-induced cardiomyocyte damage (48). Direct consumption of pomegranate has also shown the beneficial effects in the cardiovascular health (50–53). In our earlier study, we found a reduction in low density lipop polysaccharide (LDL) in the Swiss-albino mice after consumption of methanolic extract of pomegranate (PME), which was induced upon ovariectomy when compared to sham control (4).

Estrogens exert anti-inflammatory activity via the receptors like ER α , ER β , and GPR-30 that are present on cardiac cells encompassing cardiomyocytes, fibroblasts, vascular endothelial, and smooth muscle cells (54), thus, being beneficial in cardiovascular diseases such as coronary heart disease, ventricular hypertrophy, atherosclerosis, etc., via nuclear or non-nuclear pathways (55, 56). The ER β appears to have a substantial cardioprotective effect (54). However, whether the protective effects of the pomegranate components or of urolithins are caused by these receptors are not investigated. It would be worthwhile to unravel whether they show similar or varying profile and benefits in different categories such as in pre-, peri- and post-menopausal women, and whether pomegranate benefits correlate their metabotype and different hormonal phases in women.

BREAST CANCER

Our previous research showed that methanolic extract of a pomegranate peel reduced breast cancer proliferation by binding to estrogen receptor without affecting uterine weight, unlike estradiol or tamoxifen (4). A plethora of evidence points to preventive possibilities of pomegranate in breast cancer at its various stages and processes of cell survival (12). We had also reported that the PME can inhibit the proliferation induced by endogenous SERM 27 hydroxycholesterol (57). From the findings so far, urolithins are active molecules, but its availability and type are dependent on the gut microbiota and, hence, the extract may have limitations in its applicability. For the first time, Larossa et al. demonstrated in 2005 that UA and UB can act as “enterophytoestrogens,” exhibiting estrogenic activity in a dose-dependent manner without antiproliferative or toxic effects. Urolithins in combination with estrogen showed antiproliferative activity and anti-estrogenic activity and thwarted the proliferative activity of estrogen in the cell line models of human breast. The competitive binding assay showed that UA had much higher affinity to both ER α and ER β than UB. The UA had a slightly higher affinity toward ER α than ER β , with half maximal inhibitory concentration (IC50) values being at 0.40 and 0.75 μ M. Skledar et al. (21) reported a comparatively higher half maximal effective concentration (EC50) value for ER α , i.e., 5.60 μ M. However, the conjugated metabolites of urolithins lacked these activities (22, 58). Hence, it is speculated that the potential antiproliferative/cytotoxic, as well as estrogenic/antiestrogenic activities, in breast tissues would

primarily depend on the metabolite formed in the specific tissues. It is also suggested that though conjugation may hinder the direct antiproliferative activity, there is a probability of a long-term tumor-senescent chemoprevention (22).

Urolithins have been documented to inhibit aromatase and proliferation of breast cancer cells stimulated by testosterone (24). Strikingly, UA and UB inhibit 17 β -hydroxysteroid dehydrogenases (17 β -HSD1) (25), an enzyme involved in dihydrotestosterone (DHT) inactivation and in the conversion of inactive estrone (E1) to estradiol (E2), and, hence, critical for estradiol synthesis. Of note, high 17 β -HSD1 mRNA expression in patients with breast cancer correlates with a weak prognosis for breast cancer, thus, enhancing the breast cancer proliferation and invasion (59). Additionally, urolithins inhibit androgen receptor (60). These results point to its ability to act as anti-estrogenic in breast cancer. The UA also suppresses hyperactivated transglutaminase TGM2 which is one of the novel gene signatures expressed in metastatic cells that have undergone induction and reversion of epithelial–mesenchymal transition (EMT) and have induced metastasis (61). Also, urolithins can cross blood brain barrier and, hence, its potential in preventing breast to brain metastasis is worth investigating, since there is very less information on anti-estrogens or aromatase inhibitors that can cross blood brain barrier, which is a potential endocrine tissue (62, 63).

ENDOMETRIAL PROTECTION

Endometrial cancer is the sixth most commonly occurring cancer in women (64). In premenopausal women, endometrial proliferation is driven by estrogen, whilst after menopause, peripheral tissues like adipose tissue takes over estrogen synthesis, which implies that obesity increases likelihood of endometrial cancer in the postmenopausal uterus (65). In this context, it is worthwhile to mention that the pomegranate and urolithins have been shown to have preventive roles in obesity (4, 66–68). Urolithins are found to inhibit human endometrial cancer cells in an *in vitro* study (20). It also modulated the expression of ER α -dependent genes like ER β , PGR, pS2, and GREB1. The UA and UB exhibited antiproliferative activity in the human primary endometriotic cells and reduced the invasion and expression of Matrix metalloproteases (MMPs) and matrix adhesion receptor. Both UA and UB were found to decrease the viability and integrity of endometriosis spheroids (69). These studies are indicative of the ability of urolithin to have protective effects on the endometrium. Endometrial cancers are mostly hormone driven *via* estrogen receptors (70) and, hence, are often a side effect of SERMs like tamoxifen (71). Therefore, SERMs which do not activate endometrial proliferation is much desired in the present clinical context. If urolithins are further explored for their activities in hormone-dependent tissue, they can be exploited for their SERM activity. Hitherto, there are only *in vitro* evidence. It is important to consider that, within the body, the urolithins undergoes the phase-II conjugation (72) and reaches the systemic tissues. These conjugates have not been studied for antiproliferative activity in the endometrial cancer. Interestingly,

the tissue level of the deconjugation of urolithin glucuronides has also been reported (72). Indeed, more concrete studies and evidence are needed to understand and to prove the real protective capacity of these compounds and their distribution with respect to endometrium and their combinatorial behavior with other synthetic SERMs.

PROSTATE WELLNESS

In 2020, prostate cancer was the second most commonly occurring cancer in men, as well as the fifth leading cause of death among men (64). It is noteworthy to mention that prostate cancer has been reported to be driven by ER α , AR, and non-genomic estrogen signaling pathways mediated by orphan receptors like GPR30 and ERR α and, hence, phytoestrogens have been shown to have a beneficial role in prostate cancer (73, 74). Pomegranate and its metabolites, ellagic acid and urolithins, found concentrated in mouse prostate, colon, and intestinal tissues (75), prevent proliferation of prostate cancer (60, 76–79). Interestingly, it has been reported that the beneficial effects of pomegranate juice against prostate cancer may be exerted by urolithin glucuronides and dimethyl ellagic acid (38). Combinatorial treatment with urolithins and bicalutamide, a clinically used non-steroidal anti-androgen, used to treat prostate cancer (80), also showed antiproliferative effects on human prostate cancer cells. Antiproliferative effects of urolithins were more conspicuous in androgen-independent than in androgen dependent cells. Antiproliferative activity of urolithins was mediated by AR through AKT signaling pathway (81) and P53-MDM2 pathway (82). Although the possible role of estrogen receptor has been proposed in other studies (80), there is still no clear evidence. Apart from this, urolithins can strengthen muscles (83), which is an added advantage while treating prostate cancer by androgen deprivation, given that this therapy can cause muscle weakness (84). If this study proves or extends its applicability in humans, urolithins could be helpful in general wellness of prostate, as an SERM, an adjuvant, or for muscle strengthening. Pomegranate and its constituents, including its colonic metabolite, have shown propitious results in prostate cancer. These findings provide very interesting leads and points to the ability of the pomegranate metabolites for the prevention of prostate cancer recurrence (85). The chemopreventive potential of pomegranate ellagitannins, coupled with the finding that urolithin metabolites accumulate in prostate, suggests that pomegranate may be a prospective therapeutic formulation in prostate cancer. Major urolithin that accumulates in the prostate after ellagitannin consumption is UA and its metabolite Urolithin A glucuronide (UA-glu). However, the concentration of these are very low, that is, in the range of ng/g albeit urolithins reach micromolar level concentrations in the bloodstream (38). Hence, the *in vitro* evidence using supraphysiological concentrations of urolithins or unconjugated urolithins might not give a realistic data on whether these metabolites can be protective in prostate cancer. Studies should be undertaken to understand the physiological levels of urolithin, or its conjugates, that can accumulate in the prostate upon consumption of urolithins at

its safe doses, and how is it beneficial in prostate cancer at these doses.

UROLITHINS A GLIMMER OF HOPE IN BONE HEALTH

Our earlier studies have shown that pomegranate has a protective role in osteoporosis (86) using MC3T3-E1 cells and ovariectomised Swiss-albino mice. The results indicated that the PME (80 µg/ml) has significantly increased the ALP (Alkaline Phosphatase) activity, in agreement with the findings of Spilmont (87), suggesting its role in modulating osteoblastic cell differentiation. This connotes its potential as a promising nutritional supplement in management of osteoporosis associated with menopause. The UA has been shown ameliorate intervertebral disc degeneration, a common cause of back pain (88) in a needle-puncture rat tail model via c-JUN and PI3K/Akt/NF-κB pathways. The UA inhibited the inflammatory molecules and debilitated the degradation of the extracellular matrix (ECM) induced by IL-1β. Both *in vitro* and *in vivo* evidence support its protective role in osteoarthritis (44). The question whether urolithins can act *via* estrogen receptors like estrogen (89) in these cells have not yet been explored. Evidence points to the potential of urolithins in promoting bone health, giving it an edge to be an ideal SERM.

NEURODEGENERATIVE DISEASE

A plethora of studies using different models have adduced that estrogens play a vital part in protecting women against stroke and neurodegenerative diseases, though the mechanisms have not been fully elucidated. All the neural cells express estrogen receptors and the neuroprotective properties are, in part, attributed to the receptor activation in multiple cell types. Microglial cells, the major immune cells that inhabit the CNS, are regulated by estrogen, which, in turn, protects the neuronal functions and prevents neurodegeneration (90). This offers the prospect of selectively targeting estrogen receptors in the treatment of neurodegenerative conditions that comes with aging and menopause. Interestingly, PE is demonstrated to act against Alzheimer's and Parkinson's disease in many studies (91–95). Presence of urolithins in brain after consumption of pomegranate has also been reported (95). Urolithins were the only compounds, among 21 others, that is isolated from the extract that met the criteria required for the penetration of blood-brain barrier (BBB) permeability (94). The β-amyloid fibrillation was averted by urolithins in an *in vitro* study. In Alzheimer's model, UA imparts cognitive protection by protecting neurons from cell death, and by triggering neurogenesis *via* anti-inflammatory signaling. In addition, it inhibits monoamine oxidase (MAO) (96), an enzyme that inactivates monoamine neurotransmitters in neurological disorders, such as depression and Parkinson's disease (97). Although the neuroprotective effects of urolithins are reported, evidence is still weak, partly due to the lack of physiologically relevant studies using the circulating conjugated urolithins that might reach brain tissues, in a nutritional context.

In 2017, González-Sarrías et al. (98) demonstrated that UA and Iso-UA, but not UB-glu, showed a slight attenuation of the H₂O₂-induced cytotoxicity in human-derived neuroblastoma SH-SY5Y cells. Another study showed that media from lipopolysaccharide (LPS)-BV-2 murine microglial cells co-culture cell model, treated with urolithins, preserve the SH-SY5Y cell viability (99), and protect neuroinflammation, although, methylated urolithins have not been detected in circulation in humans, so far. Thus, to date, only limited studies were performed with conjugated urolithins in the context of neuronal protection. Notably, SERMs like tamoxifen and raloxifene are known to regulate the functions of astrocytes, neurons, and microglia *via* ERα and the ERβ and G-protein coupled estrogen receptor (GPR30) (100). Hence, it would be interesting to unveil the potential of the urolithins to act as estrogen receptor modulators in the neuroimmune axes.

AGING AND MUSCLE STRENGTH

Ryu et al. (83) found that feeding of *C. elegans* during entire lifetime, i.e., from eggs until death with 50 µM of UA, UB, UC, and Urolithin D (UD), has extended the lifespan by 45.4, 36.6, 36, and 19.0%, respectively, and was dose dependent. However, the treatment with ellagic acid had no effect. Mitophagy induced by urolithins in mammalian cells, *C. elegans*, and rodents culminated in the improvement of the overall health. The short duration of urolithin administration in young worms and mammalian cells reduced the mitochondrial content without affecting the maximal respiratory capacity. This proved that despite the decrease in the mitochondrial pool after UA treatment, the remaining mitochondria are robust and meet the energy requirement. A long-term UA administration in rodents induced mitochondrial biogenesis and mitophagy in the muscles of both young and old animals. The UA, at a dose of 50 mg/kg daily in aged mice which is equivalent to 4 mg/kg in humans, improved the age-related muscle decline, as well as the muscle strength suggesting its potential for treating an impaired muscle functionality. This dosing is within standard dosing regimens used for both nutrition and pharmaceutical active ingredients. Urolithins may also have different mechanisms which regulate the mitochondrial biogenesis or mitophagy, since they are known to have an estrogen receptor binding affinity. Both UA and UB regulate skeletal muscle mass also by enhancing synthesis of protein and inhibiting the ubiquitin-proteasome pathway (101). The UB can produce muscle hypertrophy and reduce muscle atrophy in mice with sciatic nerve denervation. Both urolithins, UA, and UB in different models have shown their capacity to enhance the muscle strength by different mechanisms, thus, implying its therapeutic and preventive potential in enhancing muscle strength in various pathological and age-related maladies. Given these, the ability of these molecules to act *via* estrogen receptors or how different is its action in females can be examined since estrogen deprivation, or its reduction with menopause (102) or ovarian failure, results in weakness of the skeletal muscle. Evidence points that estrogen improves the mitochondrial membrane microviscosity and the bioenergetic function in skeletal muscle (103) and in muscle proteostasis. It

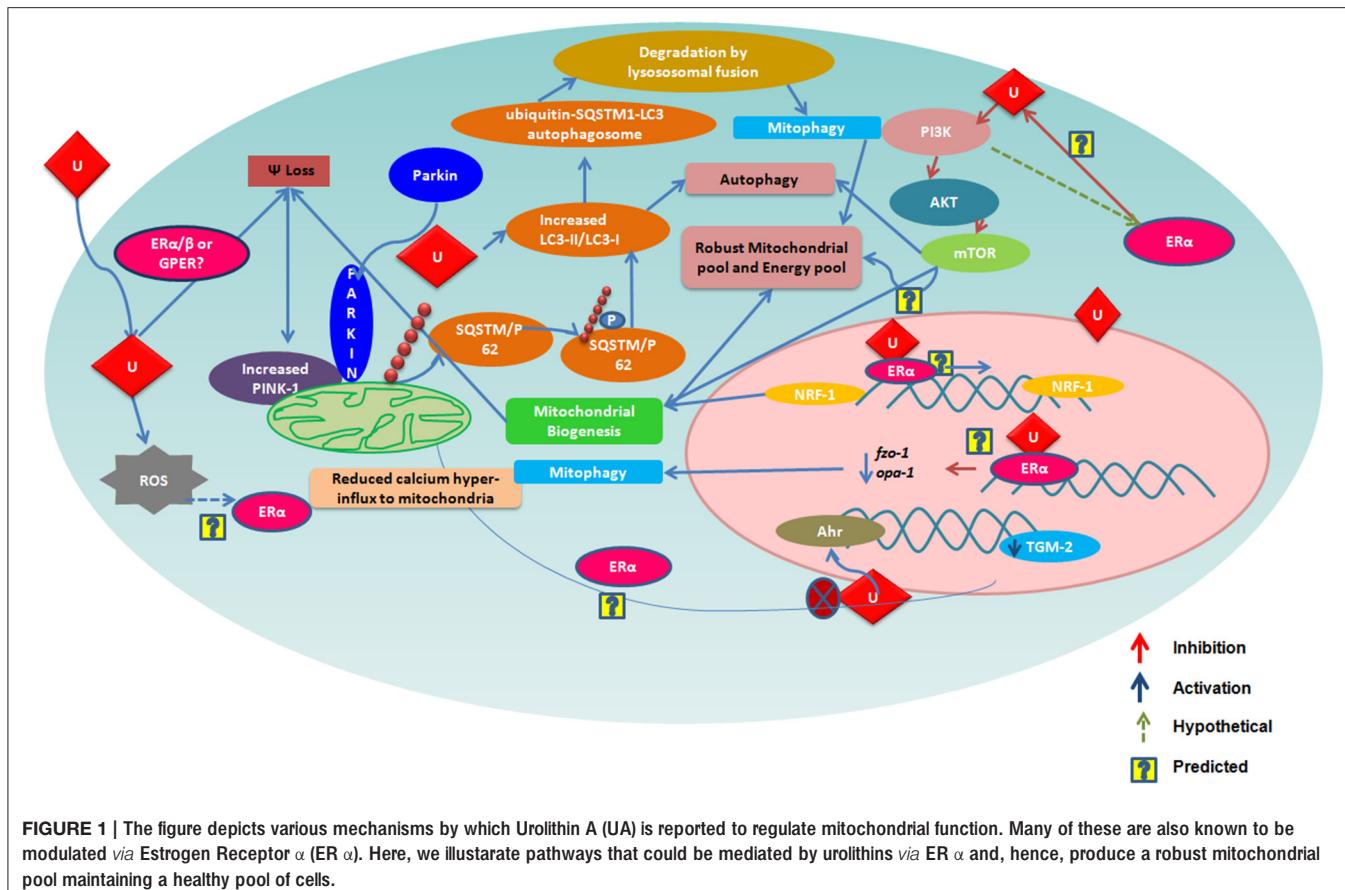


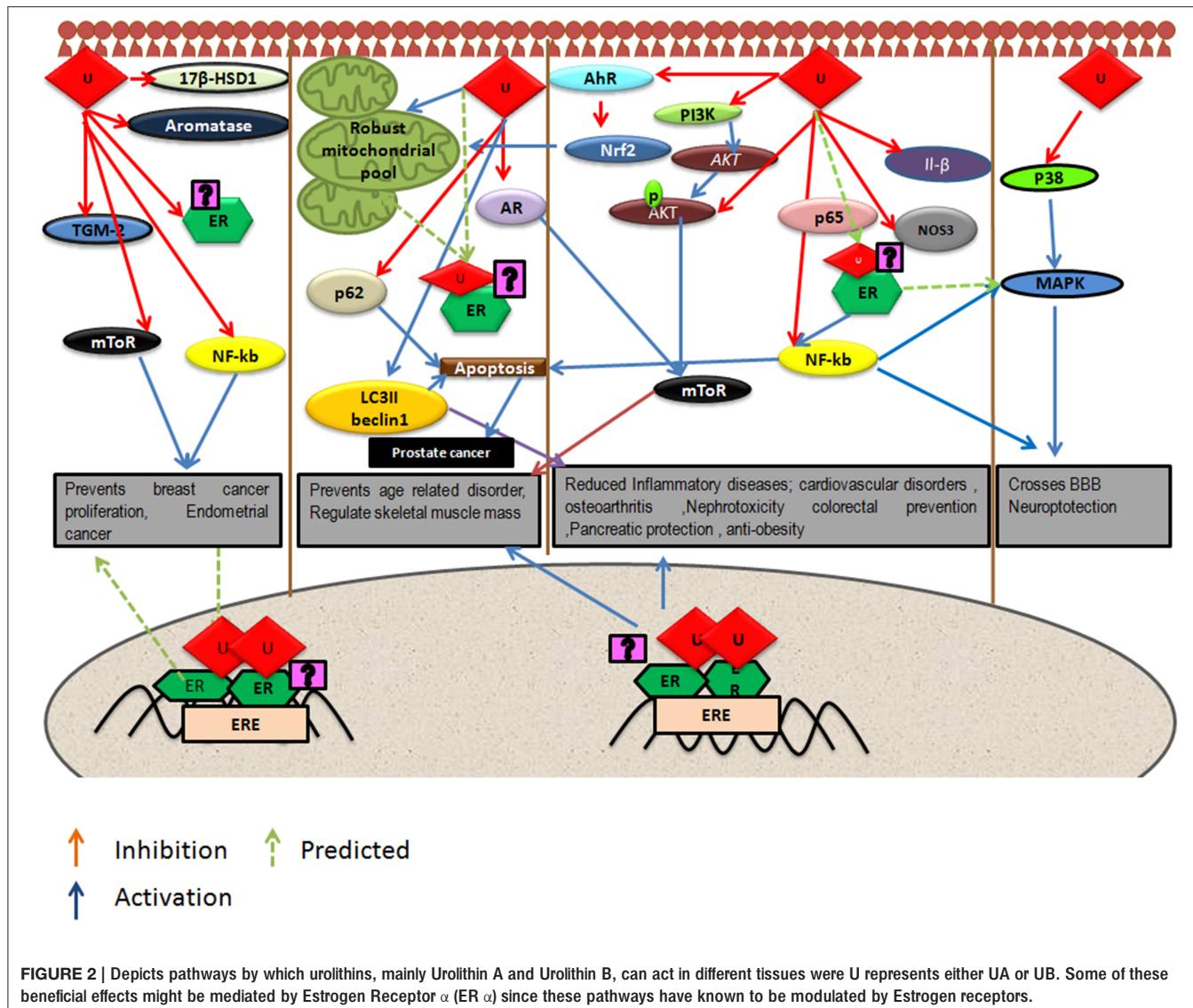
FIGURE 1 | The figure depicts various mechanisms by which Urolithin A (UA) is reported to regulate mitochondrial function. Many of these are also known to be modulated via Estrogen Receptor α (ER α). Here, we illustrate pathways that could be mediated by urolithins via ER α and, hence, produce a robust mitochondrial pool maintaining a healthy pool of cells.

also increases the collagen content of tendons and ligaments. Nevertheless, it must be noted that these benefits come at the cost of a decreased connective tissue stiffness (104). It would be intriguing to know whether urolithins can take over the function of estrogen in its absence.

MITOCHONDRIAL REGULATION BY UROLITHINS

Urolithins can induce mitophagy (83) and mitochondrial biogenesis in aged animals; the final consequence being the improvement of organismal phenotype and maintenance of maximum respiratory capacity emphasizing potential of urolithins having a dual role to maintain healthy mitochondria. The role of estrogen receptors in mediating this effect has not been investigated. The UA was found to induce PINK-1 and has increased the biomarkers for autophagy and mitophagy with ubiquitination of p62/SQSTM. Cells have developed sophisticated and elaborate mechanisms to adapt to stress conditions and alterations in metabolic demands, by regulating mitochondrial number and function by the generation of new mitochondria and by the removal of damaged or unwanted mitochondria for the maintenance of mitochondrial and cellular homeostasis (105). This implicates that urolithins could help

in preventing many pathological conditions resulting in or caused from damaged mitochondria or failed mitochondrial metabolism. It has been reported that UA exert gut barrier functions through activation of aryl hydrocarbon receptor (AhR)-nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent pathways to upregulate epithelial tight junction proteins (40). The UA inhibits transglutaminase type 2 (TGM2)-mediated mitochondrial calcium influx, which alleviates high glucose-stimulated amyloidogenesis and neuronal degeneration (106), thus, regulating mitochondrial and calcium homeostasis. Tamoxifen, a SERM, is also known to target mitochondria by ER-dependent and independent pathways. Further, the tamoxifen-resistant cells are known to display altered mitochondrial pathways with increased mitochondrial content like many other cancer drugs (107). It has been seen that drug resistance can be overcome by modulating estrogen–estrogen receptor-mitochondrial pathway. Estrogen (108) via ERs is involved in the life cycle of mitochondria and controls the mitochondrial biogenesis, mitochondrial quality control, and mitophagy (108, 109). Examining whether urolithins can modulate mitochondrial pathways via estrogen receptors can help better understand its potential. The **Figure 1** consolidates the estrogen mediated mitochondrial pathways and how urolithins, through ERs could or by other mechanisms, can possibly act in a similar way. Thus, urolithins by different molecular pathways exert beneficial effects



in multiple tissues, but whether these effects involve estrogen receptors remain elusive. **Figure 2** shows the different pathways via which urolithins act and how estrogen receptor could be part of these mechanisms.

CORONAVIRUS DISEASE (COVID-19)

Clomiphene and toremifene SERMs are reported to have potent inhibitory activity in filovirus infections like EBOLA infection (110), while raloxifene hydrochloride and quinestrol inhibit flaviviruses such as Zika virus in ER-independent pathways (111). Use of SERMs in the cytokine storm and in the inflammation associated with COVID-19 is suggested as a promising pharmacological option (112). One of the main reasons that the COVID-19 is a threat to global health is due to the lack of targeted therapeutic agents. Out of the several coronavirus proteins proposed as druggable targets,

3-chymotrypsin-like protease or main protease (Mpro), a non-structural protein that breaks down the viral polyproteins to generate other non-structural proteins, the RNA-dependent RNA polymerase and helicase, is considered pivotal (113). Given this, it is interesting to note that urolithin metabolites can exert a mild anti-SARS-CoV-2 Mpro inhibition (113) at physiological relevant concentrations ($2\text{--}50 \mu\text{M}$), detectable in human colon tissues after consumption of hydrolyzable tannin-rich foods, as per clinical studies (114). Also, the pomegranate peel extract, punicalin, punicalagin, and UA have the potential to block the SARS-CoV-2 spike (S) glycoprotein receptor-binding domain (RBD)-ACE2 receptor on host cells contact, which is one of the first steps of virus infection (115). Additionally, it has been understood that SARS-CoV-2 can activate pro-inflammatory chemokines in the early stage, and this can lead to the development of either a protective immune response or an exacerbated inflammatory response

TABLE 1 | The table consolidates the relevant studies related to Urolithins and their significant outcome.

Urolithin type	Activity/ disease tested	Model	Concentration	Effects	Molecular target/pathway	Conclusion	Reference and year
UA and UB	Estrogenic/Anti-estrogenic	MCF-7	0.1–40 μ M	Proliferative, but prevents E2 induced proliferation. Binds to ER α and ER β with different affinity. UA has higher affinity	Estrogen receptors	UA and UB have estrogenic and anti-estrogenic activity	Larrosa et al., 2006 (19)
UA	Colon inflammation	Male Fischer rats induced with acute colitis by dextran sodium sulfate	UA:15 mg kg/ day	Pomegranate extract and UA decreased inflammation markers and favorably modulated the gut microbiota. UA preserved colonic architecture	UA decreased inflammation markers like iNOS, cyclooxygenase-2, PTGES, and PGE2 in colonic mucosa	UA probably the most active anti-inflammatory compound derived from pomegranate ingestion in healthy subjects, while in colonic inflammation group the effects may be by non-metabolized ellagittannin-related fraction	Larrosa et al., 2010 (37)
UA, UB, mUA, mUB	Alzheimer's disease	<i>In silico</i> , <i>C. elegans</i>	10–100 μ M 10 μ g/ml for 40 h	Urolithins passes BBB criteria, urolithin reduces A β fibrillation mUB protected <i>C.elegans</i> from A β induced neurotoxicity and paralysis	NA	Urolithins can reduce A β fibrillation	Yuan et al., 2015 (94)
UA	Prostate cancer	LNCaP cell line	40 μ M	UA increase cells in G1-phase, induction of apoptosis	UA upregulates CDKN1A	A potential chemopreventive agent for prostate cancer	Sánchez-González et al., 2016 (79)
UA and UB	Endometrial cancer	ECC1, Ishikawa cell	0.1–50 μ M	Antiproliferative, G2/M arrest, ER α modulation	Cell cycle proteins, suppresses ER α , enhances ER β , and PGR, Ps2, GREB1, down GRIP1	Antiproliferative in endometrial cancer	Zhang et al., 2016 (20)
UA, UB, UC, and UD	Lifespan extension	Bacteria: <i>E. coli</i> , C2C12 myoblast, K intestinal cell <i>C. elegans</i> , Sprague-Dawley rats C57BL/6J	25–50 μ M, 8 h 10–50 μ M, 4–24 h 50 μ M till death, 25 mg/kg/d–7days, 50 mg/kg/d–34 weeks	Mitophagy induction Improved pharyngeal pumping rate and mobility, better maintenance of muscle fiber organization, mitophagy induction, decreased mitochondrial content while maintaining maximum respiratory capacity, long term exposure induced mitochondrial biogenesis	UA lowered <i>fzo-1</i> and <i>opa-1</i> : Important in mitochondrial fusion machinery UA acted via genes <i>bec-1</i> , <i>sgst-1</i> and <i>vps-34</i> , and the mitophagy genes <i>pink-1</i> , <i>dct-1</i> and <i>skn-1</i> (<i>Nrf2</i>) homolog	UA improves mitochondrial and muscle function	Ryu et al., 2016 (83)
UA, UB, UC	Pheochromocytoma	PC12 cells	10–300 μ g/ml	UC treatment increased lactate dehydrogenase release and membrane lipid peroxidation, and induced cell apoptosis, cell cycle arrest at S phase, and Reactive oxygen species (ROS)	Apoptosis Pathway: Bcl-2/Bax caspase 9 and caspase 3	UC, showed potent cytotoxicity in PC12 cells compared to EA	Yin et al., 2017 (125)

(Continued)

TABLE 1 | Continued

Urolithin type	Activity/ disease tested	Model	Concentration	Effects	Molecular target/pathway	Conclusion	Reference and year
UA and UB	Diabetic cardiomyopathy	Wistar rats induced with type-II diabetes	2.5 mg/kg /day: IP 3 weeks	Prevented early response of cardiac cells to hyperglycemia, improved myocardial microenvironment, and maximal rate of ventricular pressure rise, recovery of cardiomyocyte contractility, and calcium dynamics	SERCA2/PLB Ratio increase and Reduced CX3CL1 when compared to diabetic group	Prevents the initial inflammatory response of myocardial tissue to hyperglycemia	Savi et al., 2017 (49)
UA and UB	Toxicity study	Human peripheral lymphocytes Wistar rats	0.0006–2.29 mg/ml 1,000 mg/kgw oral, 2.5 mg/kg bw i.v	No changes or frameshifts No gene mutations by base pair 28- and 90-day study: Non-genotoxic, no change in clinical chemistry, hematology, or urine analysis. No toxicity observed at any target organ	NA	The NOAEL was the highest dose tested, 5% UA by weight in the diet, or 3,451 mg/kg bw/day in males and 3,826 mg/kg bw/day in females	Heilman et al., 2017 (27)
UA, UA, UB	Skeletal muscle mass	C2C12 myotubes Twelve-week-old male or female C57/Bl6 J mice	15 μ M 10 μ g/day of urolithin B during 28 days	UB not UA enhances differentiation of C2C12 myotubes UB induces muscle hypertrophy, reduces muscle atrophy	Represses ubiquitin proteasome pathway. crosstalk between the AR and the mTORC1 pathway, possibly via AMPK	UB has potential for the treatment of muscle mass loss	Rodriguez et al., 2017 (101)
UA and EA	Cisplatin-induced nephrotoxicity	Male Sprague Dawley rats	50 mg/kg body weight-5 days	UA reduced creatinine and tubular apoptotic cells in Cisplatin-induced kidney damage Reduced macrophage infiltration	Reduced NF- κ b and NOS3, Iba1 induced by cisplatin in kidney	UA mitigates cisplatin-induced nephrotoxicity in rats	Guada et al., 2017 (117)
UA, UB, UC	Prostate cancer	LNCap cells	10–40 μ M	Urolithins inhibited proliferation of LNCaP prostate cancer cells. The mixtures of bicalutamide with UA and UB had additive anti-proliferative effect. Combinations of bicalutamide with UA and UB had attenuated pro-apoptotic activity	NA	The differences in activity of urolithins in prostate cancer imply health benefits and interactions will depend on the type of produced ellagittannins metabolite	Stanislawska et al., 2018 (80)
UA	Anti-inflammatory potential in macrophages	J774.1 murine macrophage HEK,293 cell lines	1–50 μ M	UA strong inhibitor of M1 (LPS) macrophage polarization, UA elevates autophagic flux in macrophages	Inhibit p65 nuclear translocation Reduced pro-inflammatory proteins and NO production Impaired Akt/mTOR signaling	Increased activity of the autophagic cellular recycling machinery aids the anti-inflammatory bioactivity of UA	Boakye et al., 2018 (118)
UA	Colorectal cancer	SW620	1–30 μ M	UA decreased cell proliferation, and cell migration, Induced autophagy, and apoptosis. Suppressed cell cycle progression	Induced LC3	UA induces autophagy and inhibit CRC cell growth and metastasis	Zhao et al., 2018 (126)
UA, UB, Iso-UA, and UA conjugates	Breast cancer	MCF-7 MDA-MB-231	1–50 μ M	Alycones exerted antiproliferative and estrogenic/antiestrogenic activities but both their glucuronide and sulfate conjugates lacked these activities	NA	Antiproliferative and estrogen receptor modulatory activity in breast cancer cells	Ávila-Gálvez et al., 2018 (58)

(Continued)

TABLE 1 | Continued

Urolithin type	Activity/ disease tested	Model	Concentration	Effects	Molecular target/pathway	Conclusion	Reference and year
UA	Effect on immune cells	Murine CD4+ T cells	5–50 μM	UA regulates of Ca ²⁺ entry into CD4+ T cells leading to suppression of CD4+ T cell activation	Upregulates the expression of miR-10a-5p which in turn decreases store-operated Ca ²⁺ entry (SOCE), by downregulating Orai1 and STIM1/2 expression	UA could be used a natural immune suppressant during various inflammatory disorders including inflammatory bowel disease	Zhang et al., 2019 (121)
UA	Alzheimers disease (AD)	PPswe/PS1ΔE9 (APP/PS1) mouse model of AD	300 mg/kg	UA ameliorated cognitive impairment, prevented neuronal apoptosis, and enhanced neurogenesis, attenuated Aβ deposition, and peri-plaque microgliosis and astrogliosis in the cortex and hippocampus	UA enhanced cerebral AMPK activation, decreased P65-NF-κB activation and P38MAPK, and suppressed Bace1 and APP degradation	UA imparted cognitive protection by protecting neurons from death and triggering neurogenesis via anti-inflammatory signaling	Gong, 2019 (96)
UA	Tissue deconjugation of UA	LPS administered male Sprague-Dawley rats	26 mg / kg b.w	Tissue deconjugation of UA-glur to UA after lipopolysaccharide (LPS)-induced inflammation	NA	Tissue deconjugation of Uro-A glur to UA after lipopolysaccharide (LPS)-induced inflammation, explaining systemic <i>in vivo</i> activity of free Uro-A in microenvironments subjected to inflammatory stimuli	Ávila-Gámez et al., 2019 (72)
UA	Mitochondrial and cellular health	Healthy, sedentary elderly individuals	1,000–2,000 mg of UA delivered orally	UA has a favorable safety profile UA bioavailable in plasma modulated plasma acylcarnitines and skeletal muscle	Mitochondrial gene modulation	UA induces a molecular signature of improved mitochondrial and cellular health	Andreux et al., 2019 (123)
UA and synthetic analog UAS03	Beneficial activities at gut epithelium	HT29 bone marrow derived macrophages Male mice (C57BL/6J; 6–8 weeks old)	Oral doses 20 mg/kg at 6–24 h	Anti-inflammatory activities and enhanced gut barrier function	Activation of aryl hydrocarbon receptor (AhR) (Nrf2)-dependent pathways to upregulate epithelial tight junction proteins	Attenuated colitis in pre-clinical models by remediating barrier dysfunction in addition to anti-inflammatory activities	Singh et al., 2019 (40)
UA	Increase availability by nanoparticle encapsulation	Male Sprague/Dawley rats	Oral gavage a single dose of 50 mg plain UA, 25 mg P2Ns UA, or 10 mg or 25 mg P2Ns-GA UA	Nanoparticle encapsulated UA led to a seven-fold enhancement in oral bioavailability. It attenuated the histopathological hallmarks of cisplatin-induced AKI and reduced mortality by 63%	Nanoparticle UA therapy downregulated Nrf2 and P53-inducible genes and involved anti-apoptotic signaling	Nanoparticles greatly increase the oral bioavailability of UA leading to improved survival rates in AKI mice, in part by reducing renal oxidative and apoptotic stress	Zou et al., 2019 (124)

(Continued)

TABLE 1 | Continued

Urolithin type	Activity/ disease tested	Model	Concentration	Effects	Molecular target/pathway	Conclusion	Reference and year
UA	Type 2 diabetes	Type 2 diabetes model was induced by HFD; and streptozotocin (85 mg/kg)	UA (50 mg/kg/d) alone or UroA-chloroquine combination for 8 weeks	UA improved symptoms of diabetic mice, pancreatic function indexes. UA decreased mitochondrial swelling and myelin-like cytoplasmic inclusions	Upregulated light chain 3-II (LC3II) and beclin1, downregulated sequestosome 1 (p62), and decreased apoptotic protein cleaved caspase3 partly by (p-Akt)-p-mTOR pathway	UA protects pancreas against diabetes	Tuohetaerbake et al., 2020 (120)
UA	Osteoarthritis	Primary chondrocytes <i>Ex vivo</i> organ culture of articular cartilage	1–15 μ M 1–7 days	No UA cytotoxicity UA protected IL-1 β induced cartilage damage. UA protective in <i>ex vivo</i> organ culture of articular cartilage	UA protected chondrocytes against IL-1 β -induced injury by activating the mitogen-activated kinase (MAPK)/nuclear factor- κ B (NF- κ B) signaling pathways	UA attenuated IL-1 β -induced cell injury in chondrocytes via its anti-inflammatory action	Ding et al., 2020 (45)
UA	Obesity	Six-week-old male C57BL/6 mice 4-week-old male leptin-deficient <i>ob/ob</i> mice	30 mg/kg	UA increases energy expenditure by enhancing thermogenesis in brown adipose tissue and inducing browning of white adipose tissue	UA enhances adipose tissue production of triiodothyronine (T3), which activates thermogenic genes PGC1a and UCP-1	UA suggested as potent anti-obesity agent	Xia et al., 2020 (67)
UA	Alzheimer's disease	SH-SY5Y cells Streptozotocin (STZ)-induced diabetic mouse model	UA:100 nM UA:2.5 mg/kg/day: 8 weeks	UA prevented A β -induced mitochondrial calcium influx, mtROS accumulation, Tau phosphorylation, and cell death in neuronal cells	UA significantly reduced high glucose-induced TGM2 expression and disrupted AIP-AhR complex.	UA may prevent diabetes mellitus associated AD pathogenesis by reducing TGM2-dependent Mitochondria-associated membranes (MAM) formation and maintaining mitochondrial calcium and ROS homeostasis	Lee et al., 2020 (106)
UA	Campylobacteriosis	Abiotic IL-10 $^{-/-}$ mice infected with <i>C. jejuni</i>	0.114 mg /kg/B.W/day	UA lowered pathogen loads in ileum, but not colon. Improved clinical outcome and less inflammatory sequelae of infection. Reduced intestinal and systemic pro-inflammatory immune responses	Lowered IFN- γ , TNF- α	Oral UA administration is a promising treatment option for acute <i>C. jejuni</i> infection	Mousavi et al., 2021 (122)
UA UB urolithin glucuronides	Anti-inflammatory activity	THP-1-derived macrophages, RAW 264.7 macrophages	40 μ M	UA was the most active metabolite in terms of LPS-induced inflammatory response inhibition	Attenuate NF κ B p65 nuclear translocation, and stimulate ERK1/2 phosphorylation	UA the most potent in inflammatory response	Bobowska et al., 2021 (16)
UA mUA UB	SARS-CoV-2, main protease (Mpro) inhibitors	Assay kit consisting of recombinant Mpro	2–50 μ M	Urolithins inhibited severe acute respiratory syndrome corona virus (SARS-CoV-2) SARS-CoV-2 Mpro (by 6.6–100.0%) and bound directly to the Mpro protein	Inhibition of Mpro	Inhibitory effects of tannins and their metabolites on SARS-CoV-2 Mpro	Li et al., 2021 (113)

The UA denotes Urolithin A, UB Urolithin B and UC Urolithin C. The mUA is methylated urolithin A, while the mUB is urolithin B.

(116). The latter one may lead to cytokine storm, which is clinically manifested by acute respiratory distress syndrome and systemic consequences like intravascular coagulation (116). As said in the earlier section of this review, UA exhibits anti-inflammatory activity in various tissues (39, 45, 117–119) by modulating proteins like NF- κ b (44, 45), and other pro-inflammatory molecules like cytokine fractalkine (49, 120). Thus, UA manifests a natural immune-suppressant profile (121). It also protects *C. jejuni* infection in mice and protects other organs including lungs from inflammatory response (122). Furthermore, a recent study illustrated tissue deconjugation of UA-glu to UA in endotoxemia, thus, increasing free UA in systemic tissues, reaching relevant concentrations, and, hence, probably imparting a higher anti-inflammatory potential (72). In the light of these findings, urolithins with its immune modulatory and anti-inflammatory activity could be exploited to reduce such exacerbated inflammatory response as well.

SAFETY ASSESSMENT

Oral administration of UA has been studied at both preclinical (27, 37, 121) and clinical level (123). Both oral and intravenous administration of urolithins showed a higher prevalence of the conjugated forms of urolithins, namely glucuronidated and sulfonated forms (27). Urolithins did not induce genotoxicity in the *in vitro* assays. The no-observed-adverse-effect-level (NOAEL) was the highest dose tested, and UA was given as 5% of the diet, or 3,451 mg/kg bw/day in males and 3,826 mg/kg bw/day in females, in the 90-day oral study. In the *in vivo* studies, the clinical parameters, blood test, or hematology did not point to any toxicity. Human randomized (123), study on the safety profile of UA in the elderly and sedentary human subjects did not show adverse effects on UA consumption in any of the oral dosing regimens. Its presence was seen in plasma and skeletal muscles. The biomarkers of mitochondrial function in the skeletal muscle and plasma metabolomics were also recorded in the study. Efforts are also being made to make urolithins more bioavailable (28, 123, 124). As mentioned earlier, the UA has also been recently recognized as GRAS for its use as an ingredient by FDA, USA. The major studies performed using urolithins has been consolidated in Table 1.

CONCLUSION

To summarize what has been discussed, so far, we propose that urolithins could be beneficial in general wellness and health. Its relevance seems more pronounced in the hormone-dependent tissues, which connote its potential in hormone or endocrine-related pathogenesis. A plethora of evidence pointedly illustrate the health benefits of urolithins in cardiovascular health, muscle strengthening, bone health, breast and endometrial cancer, aging, brain related diseases, and pathologies stemming

from an inflammatory response or its consequence like in the case of COVID-19 infection. Many of these may involve the hormone receptor estrogen receptors along with the other pathways. The mechanism of action of urolithins, mediated *via* estrogen receptors, is very sparsely studied. Competitive binding studies and transactivation assays point to its ability to act as an estrogen agonist. However, it is known that estrogen receptors exhibit a complex and dynamic activity depending on the different conformation it attains according to the ligand structure and binding. It depends on the tissue it acts since the co-factors available and recruited by estrogen receptors vary between the cell types. Albeit estrogen receptor agonists, antagonists and SERMS can activate or repress unique genes, they can also trigger or repress similar subset of genes. Ergo, urolithins need to be examined for its responses in different hormone responsive tissues; its potential as estrogenic and endocrine disruptors, and whether the known health benefits involve an ER-mediated action. Urolithins, or its source, which include ellagitannin-rich food like pomegranate and the bacteria responsible for its production, could also serve as supplement as probiotics. Also, studies can be undertaken to illustrate the potential of urolithins at a clinical level on how these molecules would act in combination with an already known synthetic SERM. Nonetheless, due to pleotropic nature of estrogen receptors, it is important to consider the potential long-term merits and the adverse effects of urolithins in the estrogen receptor-dependent tissues. Taking together the recent research on urolithins, we propose this could serve as an endocrine modulator and that further investigations in this direction need attention.

AUTHOR CONTRIBUTIONS

RV and SS conceived the idea of the article. RV and VR screened and retrieved the data and prepared diagrams. RV prepared the manuscript draft. RV, AS, TS, RA, PM, and LL tabulated various studies. SS reviewed and corrected the manuscript. All authors read and approved the final manuscript.

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Review Article

Probiotic Bacteria for Healthier Aging: Immunomodulation and Metabolism of Phytoestrogens

José María Landete, Pilar Gaya, Eva Rodríguez, Susana Langa, Ángela Peiroté, Margarita Medina, and Juan L. Arqués

Departamento Tecnología de Alimentos, Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA), Carretera de La Coruña Km 7, 28040 Madrid, Spain

Correspondence should be addressed to Juan L. Arqués; arques@inia.es

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Age-related degeneration gives rise to a number of pathologies, many of them associated with imbalances of the microbiota and the gut-associated immune system. Thus, the intestine is considered a key target organ to improve the quality of life in senescence. Gut microbiota can have a powerful impact in the deterioration linked to aging by its nutritional and immunomodulatory activity. Reduced numbers of beneficial species and low microbial biodiversity in the elderly have been linked with pathogenesis of many diseases. A healthy lifestyle with an elderly customized diet including probiotics can contribute to reducing the chronic proinflammatory status and other age-related pathologies. Beneficial effects of probiotic lactic acid bacteria and bifidobacteria to alleviate some of these disorders based on their immunomodulatory properties as well as their capacity to produce bioactive metabolites from dietary phytoestrogens are summarized. On one hand, the preservation of gut barrier integrity and an increased ability to fight infections are the main reported immune benefits of probiotics. On the other hand, the intake of a diet rich in phytoestrogens along with the presence of selected probiotic bacteria may lead to the production of equol, enterolignans, and urolithins, which are considered protective against chronic diseases related to aging.

1. The Aging Process

The time-dependent biological complex processes that produce a gradual generalized deterioration of the anatomy and physiological functions of organisms are defined as aging. It led to weakness to environmental stress and therefore increases the risk of disease and death. Among multicellular organisms, aging is marked by a progressive decline in the function of multiple cells and tissues. Apparently, the event of aging is genetically determined and modulated by the environment, but the causes of those irreversible changes are still an unresolved challenge. Understanding aging is an important objective that may help to modify the aging process or the senescence effects. The aging rate could be determined by two major circumstances: the accumulation of damage and the effectiveness of somatic maintenance mechanisms [1]. Nine cellular and molecular hallmarks of aging have been proposed by López-Otín et al. [2], which are genomic

instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. In human cells, the presence of telomerase suggests that cells may be programmed to undergo senescence as a mechanism to “count” cell divisions, although stress and damage accumulation are also important for the telomere shortening [3].

The main aim of aging research is to improve the quality of life. Age-related degeneration gives rise to a number of pathologies, such as osteoarthritis, atherosclerosis, lung emphysema, malignancies (gastrointestinal, prostate), and dementias. The aging process is dependent on antistress responses, which act as antiaging mechanisms. Furthermore, immunosenescence, which can be defined as a decline in the functionality of the immune system, contribute to a chronic state of basal inflammatory activity (inflammaging) [4–6].

The most studied and reproducible nongenetic intervention in aging research is dietary restriction. However, the importance of diet composition has been highlighted when applying a reduction in calorie intake to regulate the lifespan [7]. Another important factor that can play a key role in senescence is the impact of the diet on the gut microbiota composition and the chronic inflammation. Thus, age-related changes in the nutritional behaviour are associated with the imbalances of the microbiota and the gut-associated immune system. A healthy lifestyle with an elderly customized diet including probiotics can contribute to reduce the chronic proinflammatory status and other age-related pathologies [8–10].

1.1. Aging and Gut. The gastrointestinal (GI) tract is characterized by its complexity, being the main and largest site for interaction with the external environment. The GI tract is covered by a single layer of epithelial cells, which are responsible for the digestion and absorption of nutrients and electrolytes, as well as homeostasis. Moreover, the gut-associated lymphoid tissue provides an important first line of defence that controls the equilibrium between tolerance and immunity against orally acquired food and microbes. The human gut contains the enteric microbiota, whose mutualistic relationship contributes to the maintenance of health, including digestion of complex carbohydrates, intestinal homeostasis, synthesis of essential nutrients and vitamins, protection against pathogens, and stimulation of the immune system [11]. Age-associated modifications of the gut cause disorders that clearly affect the quality of life of elderly population, becoming a major cause of morbidity [12].

A distinguishing characteristic of the aging gut is the overexpression of proinflammatory cytokine IL-6, which has an effect on the intestinal barrier function and mucosal immune system [13]. Persistence of inflammaging can also facilitate cancer development and progression [6, 14]. During postmenopause/andropause periods IL-6 levels are increased. Overexpression of IL-6 might have important ramifications with regard to both impaired immunity and intestinal barrier integrity, which can downregulate innate immunity to pathogens and consequently increase the susceptibility to infections in the elderly. Moreover, those changes in the intestinal permeability could be crucial in the development of local (celiac disease, colorectal cancer, or inflammatory bowel disease) and systemic diseases (diabetes, chronic heart failure, or obesity) and even in central nervous system disorders [15, 16].

Physical and immunological impairments of intestinal barrier are correlated with age-related diseases and lifespan. The cross-talk between gut microbiota and the gut-associated lymphoid tissue has a powerful effect on the host immune response which can lead to systemic metabolic effects [17]. Thus, the intestine is a key target organ to improve the quality of life in senescence [18, 19].

1.2. Impact of Gut Microbiota on Aging. Alterations in morphology and physiological functions modify the physical environment of the elderly gut, which affect the composition of the intestinal microbiota. Moreover, antibiotics are still an

irreplaceable therapy for the elderly, which have also a huge influence on the intestinal microbiota composition. Dysbiosis is associated with various metabolic, infectious, and inflammatory disorders including malnutrition, diabetes, bowel diseases, *Clostridium difficile* infections, obesity, colon cancer, and atherosclerosis [20, 21]. An interesting clue to unravel the role of gut microbiota in some aged-related diseases is the big interindividual variations among older subjects compared to the adults [8, 22].

Gut microbiota has a strong impact in human physiology and, therefore, on the health status in the elderly and age-related diseases [23]. Its immunomodulatory properties could help in two main aspects of aging as immunosenescence and inflammaging. Aging can be considered as an immune disorder [24]. Commensal bacteria can modulate the host inflammatory response, mainly by targeting NF- κ B. It has been proposed that an increased presence of IL-6-inducing bacteria in the elderly could be associated with elevated intestinal levels of IL-6 in the gut and therefore at systemic level [14]. Thus, an aged-type microbiota shows a low microbial biodiversity, enriched in pathobionts and facultative anaerobes and depleted of *Firmicutes*, which is linked with an increase of proinflammatory signals [22, 25–27]. Another important aspect to address during the aging process is the interaction between the microbiota and the metabolism of dietary components and their potential beneficial effects in the generation of bioactive nutrients [28, 29].

Host age, health status, and environmental factors can modulate our microbiota composition. Improving the profile of the gut microbiota during human aging, mainly lifestyle factors and nutritional habits, would have an impact on human health and longevity since longevity process is associated with human gut microbiota changes [30]. The role of gut microbiota in human aging include two main aspects: immunomodulatory and nutritional (energy availability and metabolism). Dietary interventions with probiotics or fecal bacteriotherapy could be employed to rationally enrich the gut microbiota of the elderly [20, 30–33].

2. Potential Beneficial Effects of Probiotics on the Aging

Probiotics can be applied to modulate the age-related gut microbiota imbalance and to introduce strains with specific health-promoting effects. The principal claimed benefits of probiotics in elderly people are prevention of diarrheal diseases, protection against pathogens, enhancement of the intestinal barrier function, improvement of gastrointestinal motility and inflammatory intestinal disorders, immunomodulatory effects, and prevention of colon cancer [34, 35].

Probiotic intervention, with or without a specific diet composition, would help to improve the microbiota functionality in order to obtain health benefits during the old age. In this context, a diet rich in phytoestrogens can be considered an interesting therapeutic approach against aging due to their estrogenic and antioxidant actions. Here we summarize two promising beneficial effects of probiotics to alleviate

some age-related pathologies based on their immunomodulatory properties as well as their capacity to produce bioactive metabolites from dietary compounds, such as phytoestrogens.

2.1. Probiotics to Improve Immune-Health. Senescence is associated with a decline in immune function and an increase in inflammation [10]. The effects of IL-6 on intestinal permeability could increase the penetration of microbes and/or toxins into the body [10, 36]. Probiotic intervention can improve some of these age-associated modifications of the immunological features [37–39]. However, despite their promising benefits, little is known about the effect probiotics on intestinal barrier and immune function.

Probiotics can exert beneficial effects on the preservation of gut barrier integrity and function stimulating the activity and growth of beneficial bacteria and regulating the expression of tight junction proteins [40–47].

Aging process affects innate immunity, with reduced activity or number of natural killer (NK) cells, and adaptive immunity, with reduced antigen-specific IgA antibody and cellular immune responses [48]. Probiotic treatments can ameliorate some of these processes modulating cytokine production, improving distribution and function of NK cells, macrophages, granulocytes, and T cells in the circulation, and enhancing mucosal and systemic antibody responses [49–51].

Lactic acid bacteria (LAB) and bifidobacteria are commonly found in the gut of humans and other animals as well as in probiotic supplements and foods. Their immunomodulatory properties can be applied in age-related disorders. Studies carried out on mice demonstrated the potential of probiotics to palliate the effects of aging on the immune system. Administration of *Lactococcus lactis* H61 or *L. rhamnosus* MTCC 5897 improved the age-associated Th1/Th2 imbalance [52, 53]. *Bifidobacterium adolescentis* BBMN23 and *Bifidobacterium longum* BBMN68 isolated from healthy centenarians enhanced both innate and acquired immunity in mice [54]. Supplementation of aged mice with the probiotic *Lactobacillus paracasei* NCC2461 improved the specific adaptive immune response, with higher IgG2a levels after antigenic challenge [55]. The strain *L. rhamnosus* CRL1505 was able to increase the peritoneal macrophages phagocytic activity and the number of intestinal IgA⁺ cells in the intestinal mucosa of aged mice [56]. Recently, the effect of *Lactobacillus plantarum* WCFS1, *L. casei* BL23, and *Bifidobacterium breve* DSM20213 on gut barrier and immunity in accelerated aging mice was investigated. That study found that age-related decline in mucus and systemic immunity can be modulated by probiotics but also highlights the risk of translating the beneficial effects of probiotics observed in young animals or humans to the elderly [57].

Several human studies also show a higher ability to fight infections following probiotic consumption. *Bifidobacterium lactis* HN019 enhanced phagocytic activity and number of NK cells in elderly subjects [51, 58, 59]. A probiotic cheese containing *Lactobacillus rhamnosus* HN001 and *Lactobacillus acidophilus* NSFM increased the cytotoxicity of NK cells in elderly volunteers [60]. Administration of yogurt containing the probiotic strain *Lactobacillus casei* DN-114001 to elderly

people reduced the length of winter infections compared to the control group [61]. Likewise, an improvement in the nutritional and immunological status of enterally fed elderly subjects was observed by the administration of a fermented milk containing *Lactobacillus johnsonii* La1 [62].

2.2. Probiotics, Phytoestrogens, and Aging. Phytoestrogens are polyphenols present in plants or foods derived from plants foods such as soya, flaxseed, cereals, vegetables, fruit, chocolate, and tea [63–65]. Phytoestrogens such as coumestans, stilbenes, ellagitannins, lignans, and isoflavones are similar to endogenous estrogen and therefore they have both antiestrogenic and estrogenic effects [66]. Intake of these compounds may be protective against chronic diseases related to aging, such as cardiovascular and bone diseases, various cancers, menopausal symptoms, and cognitive function [67–73]. These health benefits from phytoestrogens consumption should be attributed to the bioactive metabolites produced by gut bacteria and to the modulation of the intestinal bacterial population [74, 75]. Thus, the intake of a diet rich in isoflavones (soybeans and soy derived foods), lignans (flax seeds, cereals, etc.), and/or ellagitannins (pomegranates, cherries, etc.) along with the presence of selected probiotic bacteria may ensure the production of equol, enterolignans, and urolithins in the gut, respectively [76–78] (Table 1). This approach should be considered in the prevention and improvement of aging-related pathologies.

The transformation of isoflavones, lignans, and ellagitannins by bacteria is an essential step because

- (1) equol, enterolignans, and urolithins are more bioavailable than their respective dietary phytoestrogens [79, 80] (Figure 1),
- (2) equol, enterolignans, and urolithins have more estrogenic/antiestrogenic activities than their precursors. The biological action of these derived compounds is mediated primarily by estrogen receptors [81], modulating hormone levels and expression of estrogen receptors [82, 83]. They may act as anticarcinogens through antiestrogenic actions competing with estradiol to bind estrogen receptors [84]. Equol, enterolignans, and urolithins have various estrogenic effects in postmenopausal women, such as decreased plasma levels of estrone and estradiol sulfate and changes in the metabolism of estrogen (from 16α-hydroxylation to 2-hydroxylation, a less carcinogenic pathway) [85, 86],
- (3) equol and enterolignans are more antioxidants than their precursors [80, 87], acting against DNA damage and lipid peroxidation. The antioxidant activities of enterolignans have also been suggested to contribute to the reduction of hypercholesterolemia, hyperglycemia, and atherosclerosis [88],
- (4) finally, equol, enterolignans, and urolithins have anti-inflammatory effects and exert antiproliferative and apoptosis-inducing activities [89, 90].

Although specific bacteria responsible for the equol, enterolignans, and urolithin production are still being investigated,

TABLE 1: Potential probiotic strains implicated in the metabolism of phytoestrogen.

Bacteria	Transformation/production	Reference
<i>Lb. rhamnosus</i> CRL981	Daidzin to daidzein	[100]
<i>Lb. plantarum</i> CECT 748T	Daidzin to daidzein	[80]
<i>Lactobacillus</i> sp. Niu-O16	Daidzein to dihydrodaidzein	[101]
<i>Lb. rhamnosus</i> INIA P540	Daidzin to dihydrodaidzein	[91]
<i>Ent. faecalis</i> INIA P333	Daidzin to dihydrodaidzein	[91]
<i>Lb. mucosae</i> EPI2, <i>Ent. faecium</i> EPI1, <i>Finegoldia magna</i> EPI3, and <i>Veillonella</i> sp. EP	Daidzein into equol	[110]
<i>Lactococcus garvieae</i> 20-92	Daidzein into equol	[112]
<i>B. breve</i> 15700 and <i>B. longum</i> BB536	Daidzein into equol	[113]
<i>B. adolescentis</i> INIA P784	Enterodiol production from flax seed	[78]
<i>Gordonibacter urolithinfaciens</i> and <i>Gordonibacter pamelaeae</i> DSM 19378T	Urolithin C from ellagic acid	[137]

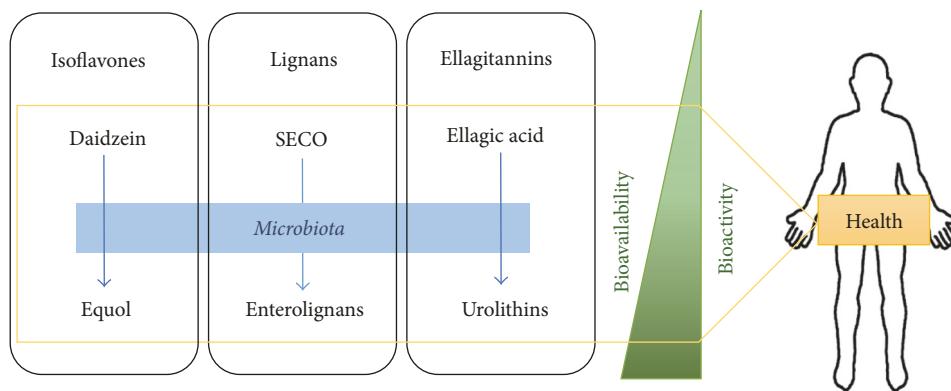


FIGURE 1: Isoflavones, lignans, and ellagitannins intake are metabolized by potential probiotic bacteria to produce equol, enterolignans, and urolithins, respectively. These compounds are more bioavailable and bioactive than their precursors.

some LAB and bifidobacteria have been involved in the metabolism of these compounds [78, 91].

2.2.1. Isoflavones, Aging, and Probiotic Bacteria. In soy and unfermented soy foods, isoflavones are as glycosides such as daidzin, genistin, or glycitin. These compounds are less estrogenic than their aglycones daidzein, genistein, and glycetein, respectively. Daidzin, genistin, or glycitin cannot be absorbed because of their higher molecular weights and hydrophilicity [92]. Then, their bioavailability requires the transformation in daidzein, genistein, and glycetein by means of β -glycosidase activities.

Benefits of soy in aging are derived from the isoflavones metabolism of bacteria, including protection against breast cancer [93], prostate cancer [94], menopausal symptoms [95], heart disease [96], osteoporosis [97], and cognitive function [98].

LAB and bifidobacteria are very important in the transformation of naturally occurring isoflavones in the form of O-glucosides, C-glucosides, or their methylated forms in the bioactive isoflavones daidzein and genistein and even

in the formation of dihydrodaidzein [91]. The capabilities of converting daidzin to daidzein have been observed in *Weissella confusa*, *Enterococcus durans* KH, and *Lactobacillus paraplantarum* KM [99], as well as in *L. rhamnosus* CRL981 [100]. *Lactobacillus* sp. Niu-O16, isolated from bovine rumen contents, converted daidzein to dihydrodaidzein [101].

Daidzein, genistein, dihydrodaidzein, and dihydrogenistein possess physiological properties of interest in healthy aging [68]. The production of daidzein and dihydrodaidzein facilitates the formation of equol and/or O-desmethylangolensin (O-DMA). Equol has enhanced effects due to its greater affinity for estrogen receptors, unique antiandrogenic properties, and superior antioxidant activity. *In vivo* and *in vitro* beneficial effects of equol have been demonstrated [102]. So, it has been possible to demonstrate *in vitro* the effect of equol against aging in skin [103] and nervous system [104]. On the other hand, the effect of equol in the improvement of menopause symptoms and in the prevention of cancers and cardiovascular diseases has been demonstrated both *in vitro* [105] and *in vivo* [106–108]. Evidence from *in vitro* studies suggests that O-DMA may have several cancer-related biological actions. However, results from human metabolic

studies and observational studies of disease risk suggest that these actions may not be physiologically relevant *in vivo* due to the amount and form (primarily glucuronide) of circulating O-DMA [109].

A mix of bacteria composed of *Finegoldia magna* EPI3, *Lactobacillus mucosae* EPI2, *Enterococcus faecium* EPI1, and *Veillonella* sp. strain EP was able to transform daidzein into equol [110]. Similarly, anaerobic incubation of *Eggerthella* sp. Julong 732 and *Lactobacillus* sp. Niu-O16 transformed dihydrodaidzein to S-equol [111], although most of equol-producing microorganisms belonging to the Coriobacteriaceae family, *Lactococcus garvieae* 20–92 [112], *B. breve* 15700, and *B. longum* BB536, were also able to produce equol [113]. LAB and bifidobacteria are also indirectly involved in the production of equol, facilitating the formation of precursor metabolites or favoring the presence of equol-producing bacteria. The administration of *Lactobacillus gasseri* influences the effect of isoflavonoids on the host, probably through changes in the gastrointestinal environment [114].

2.2.2. Lignans, Aging, and Probiotic Bacteria. Lignans, which are the major phytoestrogens occurring in Western diets, have relevant health properties [115]. However, plant lignans are not usually absorbed and must be metabolized to enterodiol and enterolactone prior to absorption [67, 116]. These compounds are the main responsible agents for the beneficial effects of lignans [117]. The transformation of plant lignans by intestinal microbiota is essential for the manifestation of these functions [118]. Enterolignans could be used in ameliorating some menopausal symptoms, protecting against atherosclerotic plaque deposition and due to their hepatoprotective effects [119–122].

Deglycosylation of the secoisolariciresinol diglucoside (SDG) present in the lignan extracts into secoisolariciresinol (SECO) is the first step towards the formation of enterolignans. The production of SECO from lignan extracts and SDG is widespread within LAB and bifidobacteria isolates [78, 123]. SDG hydrolysis is an important feature in probiotic bacteria to enhance the release of SECO, improving its bioavailability for absorption by colonic mucosa and/or the biotransformation to enterodiol and enterolactone by intestinal microorganisms [118, 124].

Nowadays, different bacteria such as *Butyribacterium methylotrophicum*, *Eubacterium callanderi*, and *Peptostreptococcus productus* and the strains *Eubacterium limosum*, *Ruminococcus productus*, *Clostridium scindens*, *Peptostreptococcus productus* SECO-Mt75m3, and *Eggerthella lenta* SECO-Mt75m2 have been involved in the production of enterolignans [65, 118]. Recently, we have described the first probiotic bacterium (*B. adolescentis* INIA P784) capable of metabolizing lignan extracts to produce enterodiol, being the first time that the production of enterolignans by a unique bacterium strain is registered [78].

2.2.3. Ellagitannins, Aging, and Probiotic Bacteria. Ellagitannins are complex derivatives of ellagic acid, which are largely metabolized by the colon microbiota of different mammals [125, 126] and humans prior to absorption [127, 128]. The

microbially mediated origin of urolithin has been demonstrated [129, 130]. Ellagittannins, ellagic acid, and urolithins exhibit anticancer properties *in vitro* and *in vivo* [69, 131]. Pomegranate extracts inhibit the growth of lung, prostate, colon, and breast cancer cells *in vitro* [132–135]. Urolithins inhibit mitogen-activated protein kinase signalling [136], which could curtail the risk of development of colon cancer by inhibiting cell proliferation and inducing apoptosis [90].

To date, only two urolithin-producing strains, *Gordonibacter urolithinfaciens* CEBAS 1/15P and *Gordonibacter pamelaee* DSM 19378, have been identified [137, 138]. However, these strains cannot produce the downstream products urolithin A and urolithin B. Unraveling the bacterial phyla or group of bacteria responsible for production of these compounds is of great interest since they can be potentially used as probiotics [139]. Consumption of foods containing ellagic acid is also associated with health beneficial effects, and they could be mediated by the presence of urolithin-producing microorganisms [77].

Probiotics able to produce or to increase species related to the production of urolithins or other phytoestrogens such as equol and enterolignans can mean a step forward in the probiotic interventions, increasing the bioavailability of these compounds, and subsequently their therapeutic applications.

3. Conclusion

Age-related changes in nutritional behaviour and microbial diversity during aging result in a higher susceptibility to infections and diseases. Likewise, the presence of some beneficial microorganisms in the gut could help to prevent or delay some age-associated diseases by improving the immune response, or by the production of bioactive metabolites as equol, enterolignans, and urolithins. The evidence for intake of probiotics along with age specifically oriented diet to improve the health during aging is promising. However, further studies for a rational manipulation of the gut microbiota are needed to better define the role of probiotics and to assess the real potential of these interventions.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Superfoods: Recent Data on their Role in the Prevention of Diseases

CHARALAMPOS PROESTOS

Department of Chemistry, Laboratory of Food Chemistry,
National and Kapodistrian University of Athens, 15771, Athens, Greece.

Abstract

By the term functional food we mean food, processed or not, which on the basis of scientific studies can contribute to the achievement of specific operational objectives within the human body and play an important role in the direction of prevention degenerative diseases and health promotion. The possible beneficial properties of functional foods are due to their content in bioactive ingredients, with specific biological properties and effects within the human body. Some examples of processed functional foods are calcium - enriched milk, enriched juices with ω-3 fatty acids, yoghurt with probiotic organisms and phytosterol-enriched margarines. At the same time, constantly new scientific findings confirm the potential beneficial properties of different conventional food, such as tea, blueberries, pomegranate, berries, hippophaes and many others, which are known by the term "superfoods". Recently, the appearance of a multitude of chronic degenerative diseases such as cardiovascular disease, diabetes, obesity, osteoporosis and cancer, has led to ways of defending human health through the adoption of appropriate dietary patterns. Hence, functional foods, provided that they fit inside hygiene and balanced nutrition, are suggested as a potential solution to reinforcing the prevention strategy, avoiding the need for therapy, with the aim of promoting the health of the population. This is the reason why there is an ever-increasing trend particularly in Europe and USA. Also, improved accessibility knowledge and information from consumers, promotes an increased search for information about their beneficial properties.



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Introduction

Conceptual Approach to Superfoods

According to literature one of the categories of functional foods, conventional functional foods,

contain bioactive compounds with specific actions within the human body. In recent years many scientific studies demonstrate the importance of a non-class processed foods whose nutritional

CONTACT Charalampos Proestos  harpro@chem.uoa.gr  Department of Chemistry, Laboratory of Food Chemistry, National and Kapodistrian University of Athens, 15771, Athens, Greece.



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composition is ideal for strengthening and promoting the proper functioning of the human body.¹ These foods are known as superfoods. Conceptually superfoods are foods that are both high in nutrition value due to a high concentration of nutrients and, on the other hand, great biological value due to satisfactory bioavailability and bioactivity within the body due to a variety of bioactive ingredients they contain.² According to Wolfe (2009),³ superfoods include foods that have a dozen or more unique properties and constitute a specific set of food stuffs, natural or medium processed with numerous nutrients. They are food that according to studies they are able to increase vitality of the human body and can be a good choice for improving the overall health by strengthening the immune system.³ The most important bioactive components of superfoods which have been proven to be beneficial to human body are polyunsaturated fatty acids (ω -3, ω -6), vitamins, minerals, probiotic micro-organisms, antioxidants, essential amino acids, polysaccharides and various enzymes. Since the most important of the superfoods properties is their antioxidant activity, among the most important antioxidants of the superfoods are mostly vitamins A, C and E, flavonoids, selenium, β -carotene, zinc, lycopene, albumin, uric acid, bilirubin, coenzyme Q10 and polyphenols such as anthocyanidins.⁴ The epidemic outbreak of a multitude of degenerative diseases has increased the need to find solutions from the natural environment, with more and more people now turning to food of high nutritional value in order to improve the quality of their life and the promotion of their health. This trend is reinforced from a series of recent scientific studies that have highlighted the importance of various superfoods such as hippophaes, Goji Berries, blueberry, spirulina, kefir, royal jelly and others.⁵ Numerous research data suggest that superfoods are a very good option to improve overall health, boosting the immune system, increasing the production of serotonin and other hormones and promoting the smooth operation of the various organic systems of the human body, but only if they are included in a balanced diet and consumed in moderation and prudence.⁶ The list of superfoods is constantly increasing year by year, while tracking valuable nutrients and understanding the mechanisms of action within the human organism have activated the scientific interest, by promoting more and more scientific research studies.⁸ In

particular, the most important superfoods according to the data obtained from several studies, are the following:⁷

- Fruits: pomegranate, berries, blueberries, raspberries, strawberries, goji berry, chickpeas, grape, acai berry, hippophae.
- Dried nuts: walnuts, almonds, cereals.
- Pulses: red beans, cocoa, sweet potatoes, mastic.
- Vegetables: broccoli, spinach.
- Seaweed: spirulina, chlorella.
- Milk products: Kefir, donkey milk.
- Herbs: ginger, ginkgo biloba, tea.
- Bee products: honey, royal jelly, waxes.

Below data of the most important superfoods according to the scientific literature are presented, such as the hippophaes, maize, blueberries, tea, kefir, maca plant, acai berries, goji berries, etc., their nutritional value, and the potential beneficial actions within the human body.

Tea (*Camellia Sinensis*)

Tea is a product of the leaves of *Camellia Sinensis* plant, which belongs to the family *Theaceae*. It's the second most popular drink worldwide after water and its study is very interested due to its consumption by plenty of people around the world. Depending on the existing industrial processing, tea is categorized into three basic types: a) fermented green tea, which is produced by drying and processing with steam of the fresh leaves of the plant. In this way, the enzymes phenol oxidases are deactivated, so that the polyphenols are not oxidised. b) Oolong tea, which is produced as its leaves plants undergo a moderate fermentation prior to drying. (c) fermented black tea, which undergoes extensive fermentation prior to drying and vaporisation. This permits the action of phenol oxidases which oxidize polyphenols to various oxidized derivatives.^{8,9,10} Fresh tea leaves contain an average of about 36% polyphenols, 25% carbohydrates, 15% proteins, 6.5% lignin, 5% ash, 4% amino acids, 2% lipids, 1.5% organic acids, 0.5% chlorophyll, and carotenoids and various other substances in less than 0.1%. The polyphenols account for 18-36% of the dry weight of the tea and are either in the form of glycosides or as free aglycones. The main polyphenols found in tea are flavonoids and phenolic acids. Of the

flavonoids, catechins make up 12-24% of its dry weight, flavonols 3-4% and anthocyanidins 2-3%.⁹ The EGCG, that is, the ester of epigallocatechin with gallic acid is the most abundant catechin in tea (8-12%) followed by epigallocatechin (EGC) (3-6%) and the gallic ester of epicatechin (ECG) (3-6%).¹⁰ The most important biological role of tea, which classifies it from many scientists in superfoods, is the intense antioxidant activity within the human organism. The main mechanisms of antioxidant action of tea polyphenols within the body is the free radical scavenging activity, complexation of ions that contribute to production free radicals and engaging in pro-oxidant regulation mechanisms and antioxidant enzyme systems.¹¹ Both green tea catechins, and black tea thioflavins bind peroxide radicals by suppressing the chain reactions and retarding lipid peroxidation.¹¹ Most clinical studies show an increase in plasma antioxidant status after drinking tea, suggesting as a possible mechanism the immediate increase of the concentration of catechins and attachment to red blood cell, and various blood components, in which they exert antioxidant effects.¹² Tea has been extensively studied for its possible action on preventing and controlling carcinogenicity. His role lies primarily in the following mechanisms:(i) Antioxidant activity and free radical scavenging, (ii) Binding of activated metabolites of carcinogens. (iii) Effect on carcinogenic elimination enzymes (detoxification enzymes), iv) Prevention of the mutation mechanisms and v) Suspension of the first step of the oncogenesis mechanism.¹³ A ten year study of 8,500 people in Japan showed that volunteers who consumed 10 cups of tea a day had 3 years later cancer compared to those who consumed 3 cups.¹⁴ Other patient control studies noted that the increased consumption of tea were associated with a reduced relative risk of cancer.¹⁵ Cancer types that have been studied more extensively are cancers of the stomach, colon, skin, lung, skin, liver, prostate and breast, while most epidemiological studies have been carried out in countries of Asia where tea consumption is higher.¹⁵ The cardioprotective effect of tea has been extensively explored and seems to be confirmed by many studies. This is related to prevention of oxidation of LDL, improvement of lipid profile, prevention of haemostasis and inflammation, inhibition of atherosclerotic procedure¹⁶ and more generally through mechanisms which relate to

the action of polyphenol-cardiovascular system. Neurological diseases and aging are associated with anxiety and increase in the concentration of various ions in the cells. Recent studies in cell cultures and animal models with neuro-illnesses have shown that antioxidant and anti-inflammatory polyphenols of tea enhance the protection of neurons of the brain and prevent cell death. The tea theanine has been shown to be able to modify serotonin and dopamine levels improving memory and learning skills while improving levels of α -waves, relaxation index and proper brain function. Studies have shown that tea consumption is associated with improvement of the symptoms of neurological diseases such as Alzheimer's and Parkinson's, mainly through action mechanisms in calcium channels, oxidant stress and AGE (Advanced Glycation Endproducts) in cerebral neurons.¹⁷ In addition to antioxidant, anticancer, cardioprotective- neuroprotective and antidiabetic therapy, the antihistaminic-and anti-inflammatory effect of tea on various tissues has been studied. The tea seems to prevent histamine-induced inflammation process and is involved in preventing allergic reactions through inhibiting the release of histamine and its deactivation enzyme protein kinase. In addition, catechins have been shown to reduce the incidence of arthritis through an effect on the endopeptidases activity, while epidemiological studies have correlated tea with bone density increase and health improvement of

Table 1: Summary of some health benefits of tea (*Camellia Sinensis*)

Health benefits	Compound/s responsible for benefits
reduced relative risk of cancer	Polyphenols, green tea catechins, and black tea thioflavins,
cardioprotective effect	Green tea catechins, and black tea thioflavins
improving memory and learning skills	Theanine
reduce the incidence of arthritis	Catechins
Neurological diseases and aging	Tea polyphenols

bone and teeth.^{10,15,17} Some health benefits related to tea consumption are presented at Table 1.

Hippophaes (*hippophae* sp.)

Hippophaes are shrubs of about 0.5 meters height that mainly thrives on land and sandy soils. The most common type is *hippophae rhamnoides* which spreads both in Europe and China. It is consumed either fresh or dried. The fresh fruit requires immediate consumption to preserve its nutrients while there is the possibility of refrigeration to increase its shelf life. The dried fruit can be maintained for long periods of time and is the most common form encountered.¹⁸ Hippophaes is considered by the scientific community to be very important due to its high nutritional value. The fruit has high vitamin C content, ranging from 114 to 1,550 mg per 100 g with an average level of 695 mg / 100 g.¹⁹ These specific levels are up to 15 times higher than orange (45 mg / 100 g). Except for an excellent source of ascorbic acid, hippophaes is rich in other nutrients such as vitamin E, amino acids, minerals (K, Na, Mg, Ca, Fe, Zn, Se), monosaccharides, organic acids, free amino acids, volatile compounds, various flavonoids (quercetin, myricetin, kaempferol) and other phenols, fatty acids, triglycerides, waxes, glycerophospholipids, phytosterols such as β-sitosterol, esters, zeaxanthin and other carotenoids and other compounds. In total, it lists more than 190 nutrients, distinguishing vitamin C, omega-3 and omega-6 fatty acids and vitamin E.²⁰ The moderate consumption of hippophaes in a balanced diet it appears to be able to offer significant

benefits to human health, most important of which are presented below at Table 2:^{18,19,20}

Blueberries (*Vaccinium Myrtillus*)

Blueberries, (*Vaccinium Myrtillus*) come from a bush of 60-90 cm height with thick branch-foliage and translucent foliage. They can be consumed as fresh fruits or dried, the latter be the most common. The dark blue-purple color is due to the high concentration of anthocyanins, that are phytochemicals with strong antioxidant action. After numerous surveys and studies, blueberries now are classified in the category of superfoods. The plethora of nutrients contained in blueberries are presented in Table 3 which refers to 100 g of fresh fruit.²¹ More and more surveys highlight their valuable contribution in health promotion, mainly because of the containing polyphenols and especially anthocyanins. It has been shown that consumption of 120 ml of blueberry juice leads to higher levels of anthocyanins in the blood compared to red and white (2.42 mmol, 2.04 mmol and 0.47 mmol, respectively), indicating the high bioavailability of their anthocyanins. The contribution of blueberries in cerebral function seems to be associated with a reduction in the risk of declaring Alzheimer's disease and other neurodegenerative diseases by reducing symptoms such as loss of balance and coordination and prevention of memory loss. Studies have shown that a quantity of 150 g of blueberries per week may contribute to reduction in blood pressure levels, and a number of other studies have shown a potential effect on the prevention of various types of cancer,

Table 2: Summary of some health benefits of Hippophaes

Health benefits	Compound/s responsible for benefits
• Enhancement of the function of the nervous system	Vitamins of the B-complex as well as all necessary for the human body minerals and trace elements (calcium, magnesium, iron, phosphorus, copper, potassium, selenium, zinc, etc.)
• Protection against cardiovascular diseases and immune enhancement	phytosterols and unsaturated fatty acids (ω-3, ω-6 and ω-9)
• Antioxidant activity: free radical scavenging	Antioxidants: flavonoids, carotenoids
• Strong anti-inflammatory, antimicrobial, analgesic, anti-inflammatory and healing action	vitamin C, omega-3 and omega-6 fatty acids and vitamin E

such as colon cancer, due to the presence of phenolic compounds, tannins, flavones and generally antioxidant ingredients. Specific studies have shown a potential inhibitory effect of flavonoids kaempferol

and luteolin in the development of ovarian cancer. The blueberries, can be included in a balanced diet, because of their low glycemic index which can regulate blood sugar levels especially in people

Table 3: Blueberries nutrient composition per 100g fresh fruit²¹

Carbohydrates	Vitamins		
Fibers	3.6 g	Vitamin A	54.0 IU
Starch	0,0 g	Thiamine (Vit B1)	0,0 mg
Sugars	14.7 g	Riboflavin (Vit B2)	0.0 mg
Sucrose	163 mg	Niacin (Vit.B3)	0.4 mg
Glucose	7,222 mg	Pantothenic acid (Vit B5)	0,1 mg
Fructose	7,355 mg	Vitamin B6	0,1 mg
Lactose	0.0 mg	Folate (Vit B9)	6.0 mg
Maltose	0,0 mg	Vitamin C	9,7 mg
Galactose	0,0 mg	Vitamin E (α -tocopherol)	0,6 mg
Proteins (amino acids)	Vitamin K		
Tryptophan	3.0 mg	Choline	6.0 mg
Threonine	20.0 mg	Betaine	0.2 mg
Isoleucine	23.0 mg	Trace elements	
Leucine	44.0 mg	Calcium	6.0 mg
Lysine	13.0 mg	Iron	0.3 mg
Methionine	12.0 mg	Magnesium	6.0 mg
Cystine	8.0 mg	Phosphorus	12.0 mg
Phenylalanine	26.0 mg	Potassium	77.0 mg
Tyrosine	9.0 mg	Sodium	1.0 mg
Valine	31.0 mg	Zinc	0.2 mg
Arginine	37.0 mg	Copper	0.1 mg
Histidine	11.0 mg	Manganese	0.3 mg
Alanine	31.0 mg	Selenium	0.1 mg
Aspartic acid	57.0 mg	Fat and fatty acids	
Glutamic acid	91.0 mg	Total fat	0.3 g
Glycine	31.0 mg	Polyunsaturated	0.1 g
Proline	28.0 mg	Total ω -3 fatty acids	58.0 mg
Serine	22.0 mg	Total ω -6 fatty acids	88.0 mg

Table 4: Summary of some health benefits of Blueberries

Health benefits	Compound/s responsible for benefits
cerebral function and reduction of neurodegenerative diseases and blood pressure prevention of various types of cancer	polyphenols and especially anthocyanins phenolic compounds, tannins, flavones, flavonoids kaempferol and luteolin
constipation and diarrhea hepatitis C virus protection and infection of the urinary tract prevention	Dietary fibers proanthocyanidins

suffering from type II diabetes, to reduce insulin resistance and act positively on people with obesity and metabolic syndrome. The presence of fibers contributes to the constipation and diarrhea, while the antioxidants proanthocyanidins have been shown to have an effect against hepatitis C virus and can prevent a possible infection of the urinary tract.²² A summary of some health benefits of Blueberries is presented at Table 4.

Royal Jelly: High Nutritional Value Food

Royal jelly is produced by young bees excreted by their subpharyngeal glands, it has creamy texture, an acidic pH and bitter taste.²³ It is a high nutritional food as it contains high amounts of proteins. Twenty nine amino acids have been identified, with aspartic acid glutamic acid being the most abundant.²⁴ Glucose and fructose are in 90% of the total sugar content, while the remaining 10% refers to various glycosides.

The fatty acids of the royal jelly act as natural antimicrobial agents while royal jelly is a good source of metals such as K, Ca, Na, Zn, Fe, Cu and Mn, with potassium being the most abundant, and B complex vitamins (B1, B2, B3, B4, B6, B7, B8, B9 and B12).²⁵ Royal jelly contains 56% water, 17% protein, 18% sugars, 4% lipids, 3% vitamins and trace elements and 2% mineral salts. Among the important features of the royal jelly is the presence of potent peptides (jelleines) that have antibacterial action. Finally, royal jelly contains satisfactory concentration of acetylcholine.²⁶ The beneficial effects of royal jelly within the human body have been recognized by a multitude of scientific studies and this is why it is included into the most important superfoods. The following data for the bioactivity and health benefits of royal jelly is obtained from the literature²³⁻²⁶ and presented below at Table 5.

Table 5: Summary of some health benefits of royal jelly

Health benefits	Compound/s responsible for benefits
Adjustment of blood glucose levels: Royal jelly appears to reduce blood glucose levels and improves lipid profile	Organic acids with insulin-like behavior in the body.
Contribution to connective, muscle and skeletal tissue.	Royal jelly contains the amino acid
Evidence suggests that royal jelly acts as a means of protecting ligaments, muscles and skin	proline necessary for the synthesis of collagen and elastin.
Improving neurological, endocrinological and metabolic disorders	Presence of pantothenic acid. high vitamin content of the B complex vitamins and acetylcholine, which acts as a neurotransmitter.
Effect on urinary and genital system	Royal jelly consumption act as an 'adrenal regulator'. During pregnancy, some cases of swelling, high blood pressure but also eclampsia were treated with royal jelly while positive effect is also observed in amenorrhea.
Elderly disorders, insomnia, increase appetite better mental and psychological functioning of the elderly.	Royal jelly has been proven to increase hemoglobin and red blood cells, resulting in the abnormal production of red blood cells (anemia) that is observed in the elderly. Responsible compounds: the vitamin B1, the phosphorus and tryptophan contained

Spirulina (*Arthrospira plantensis*)

Spirulina is an edible seaweed of fresh water with blue-green color, due to natural pigments contained therein.²⁷ The scientific name is *Arthrospira plantensis* and is growing mainly in alkaline lakes rich in metals and metalloids. Spirulina consists

of 55-70% proteins, 15- 25% carbohydrates, 6-8% fat, 3-4% fiber, while the remaining percentage is divided into metals (iron, potassium, magnesium, etc.), trace elements and vitamins (A, B, E, K) (Table 6). Spirulina contains more than 100 nutrients and is the richest plant source of protein, it has a very

Table 6: Spirulina nutrient composition per 100g²⁸⁻³⁰

Basic Nutrients	Metals / Trace Elements
Protein (g)	62.9
Total Fat (g)	3,8
Polyunsaturated (g)	1.03
Monounsaturated (g)	2,4
Carbohydrates (g)	8,4
Sugar (g)	<0,5
Edible Fibers (g)	6.9
Aminoacids	
Isoleucine (g)	3.41
Leucine (g)	5.29
Lysine (g)	2.7
Methionine (g)	0.78
Phenylalanine (g)	2,8
Threonine (g)	2.98
Tryptophan (g)	1.16
Valine (g)	3.66
Histidine (g)	0.93
Alanine (g)	4.92
Arginine (g)	4.07
Asparagine Acid (g)	5.66
Cystine (g)	0.18
Glutamic Acid (g)	8.05
Glycine (g)	3.08
Proline (g)	2.31
Serine (g)	2.87
Tyrosine (g)	2.73
Vitamins	
Protamine A (carotene) (mg)	60.1
Vitamin B1 (thiamine HCl) (mg)	5.3
Vitamin B2 (Riboflavin) (mg)	2.44
Vitamin B3 (Niacin) (mg)	10.8
Vitamin B5 (Pantothenic Acid) (mg)	1.07
Biotin (μg)	44
Folic Acid (μg)	827
Vitamin B6 (Pyridoxine) (μg)	549
Vitamin B12 (cyanocobalamin) (μg)	182
Vitamin E (mg)	7.78
Inositol (mg)	8.24

Fatty acids

γ-Linolenic (C18: 3) (mg)	1.960.4
γ-Linolenic (C18: 3) (mg)	311.2
Linoleic (C18: 2) (mg)	138.7
Palmitic (C16: 0) (mg)	735.3
Oleic (C18: 1) (mg)	157.3
Myristic (C14: 0) (mg)	85.9
Capric (C10: 0) (mg)	61.2
Laureate (C12: 0) (mg)	59.3
Palmitoleate (C16: 1) (mg)	48.6
Stearate (C18: 0) (mg)	48.3
Arachidate (C20: 0) (mg)	42.2

good source of vitamin B12 and phytochemicals with strong antioxidants properties. Continuous studies confirm that spirulina contain high and wide range of different group of nutrients. Its characterization as superfood is due both to autonomous action of the numerous nutrients it contains (Table 7), but also to the harmonic natural synergy of these compounds.^{28,29,30}

One of the most beneficial properties of spirulina is its effect on blood glucose level. From a range of clinical studies in patients with type II diabetes mellitus, it has been proven that 2g spirulina consumption on a daily basis for four months, led to gradual reduction of glucose levels, while a similar decrease was observed in other markers, such as glycosylated hemoglobin (HbA1c).^{29,31} Another documented action of spirulina is the effect on the respiratory system. Consumption of 1 g of spirulina from patients for four months, or in combination with appropriate medication or by itself appears to contribute to substantially improve of pulmonary function and reduce of levels of immunoglobulin E (IgE). The high content of spirulina in γ -linolenic acid and antioxidants, appears to contribute to

the enhancement of immune system through the stimulation of phagocytosis, the effect of production of cytokines, chemokines and other inflammation mediators, antibody production by B-lymphocytes and HIV proliferation of T-lymphocytes. This demonstrates the regulatory role of spirulina in the functioning of the immune system by enhancing the immune response and preventing over-activity of macrophages.^{32,33,34} In other studies, a possible antiviral effect of spirulina has been demonstrated on human HCV, measles, parotitis, influenza A4, HIV, and enterovirus. The mechanism of action of the spirulina against the viruses is primarily found in preventing their penetration into the host cell via the spirulina polysaccharide spirulan.^{28,34} The antimicrobial action of spirulina in the presence of alpha-linolenic and linoleic acid, and its antioxidant action is recognized by the presence of antioxidant ingredients such as β -carotene, vitamin E, selenium and polyphenols.³⁵ All health benefits are summarized at Table 7.

Maize

Maize is an ancient cereal of high nutritional value. For thousands of years maize remained the main

Table 7: Summary of some health benefits of Spirulina

Health benefits	Compound/s responsible for benefits
effect on blood glucose level, pulmonary function	Low carbohydrate, sugars
Immune system enhancement	γ -linolenic acid and antioxidants
Antiviral effect	polysaccharide spirulan
Antimicrobial and antioxidant activity	β -carotene, vitamin E, selenium and polyphenols

Table 8: Summary of some health benefits of maize

Health benefits	Compound/s responsible for benefits
nutrients absorption and inflammation suppression	soluble proteins, fiber and monounsaturated fatty acids
immune system strengthening	lysine, a basic amino acid and rhodanine
antidepressant action	high inorganic content and especially magnesium
Vision strengthening and protection	provitamin A and vitamine E
Improvement of the lipid profile and regulation of blood sugar levels	high fiber and amino acid content

consumed cereal in Middle East and North Africa. The key attribute which distinguishes it from other cereals, such as wheat, is its very small gluten content and the different quality of it. Also, it has high levels of lysine, making products more digestible. It is probably a form of two-granule wheat (*Triticum turgidum ssp. dicoccum*), while it contains valuable nutrients with multifaceted benefits for the human organism, which characterizes it as a superfood.³⁶ Compared to wheat, it contains less saturated fatty acids, while at the same time it has higher amounts of soluble proteins, fiber and monounsaturated fatty acids. Maize due to the aforementioned composition and especially proteins, inorganic compounds and fibers it appears to contribute to the absorption of nutrients and suppression of inflammation. It contains lysine, a basic amino acid that strengthens the immune system and is important for brain function. It also contains high amounts of magnesium, copper, manganese, zinc, cobalt and others metals and trace

elements.^{37,38} The basic feature of this type of wheat is the absence of allergens and the presence of a small amount of gluten. Studies have shown that maize's inclusion in diet can offer benefits that focus on the following points:³⁶⁻³⁸ A summary of maize health benefits is presented at Table 8.

Kefir

Kefir is a fermented beverage milk, extremely refreshing, tasty, easy to digest and healthy. It is one viscous drink, foaming and sour with harsh taste. Kefir is produced by a lactic and alcoholic fermentation from a wide variety of microorganisms. Thus, it is considered superior to yoghurt that has been produced only by lactic fermentation. Russian scientists worked on the nutritional value of kefir and they have proven its beneficial properties. Kefir is superior to the other acidic milk products with regard to its action against microorganisms which enter the digestive tract with food and water, due to the presence of acetic acid producing bacteria and contained yeasts. It also shows intense hydrolysis of proteins and therefore high concentration of amino acids and peptides in the intestine, plus increased amounts of vitamin B complex.³⁹ A characteristic feature of kefir is the presence of carbon dioxide (CO₂) which contributes to the formation of a finely divided gel, therefore its components can better be in contact with digestive tracts liquids and be better absorbed. Kefir due to its special taste and its microorganisms, it promotes the secretion of enzymes from the stomach and the pancreas and thus facilitates digestion and peristaltic bowel movements and therefore the passage of food from the intestine.

The contribution of kefir to improve human health is recognized by the fact that it displays higher levels of assimilation from the human body against yoghurt, as it provides beneficial bacteria, yeasts, vitamins, minerals (Table 9) and proteins of high biological value. Kefir is a balanced superfood as it appears to boost the immune system, relieves intestinal disturbances and generally contributes to a healthy digestive system.³⁹ Kefirs' beneficial yeasts and bacteria consume most of the lactose of milk so it is an ideal food for sufferers from lactose intolerance. The increased presence of calcium, magnesium and phosphorus (Table 9) contributes to the proper growth of cells and the maintenance of

Table 9: Kefir nutrient composition (mg per 100g)⁴⁰

Vitamins and minerals (mg per 100 g)	
Calcium	120
Phosphorus	100
Magnesium	12
Potassium	150
Sodium	50
Vitamin A	0.06
Carotene	0.02
Thiamine	0.02
Vitamin B2	0.17
Vitamin B6	0.05
Vitamin B12	0.005
Phosphoric acid	0.0095
Niacin	0.09
Vitamin C	1
Vitamin D	0.08
Vitamin E	0.11
Iron	0.05
Copper	0.012
Molybdenum	0.0055
Magnesium	0.005
Zinc	0.36

good body health. From the existing research data, kefir's properties for human health seem to focus on the following points:⁴¹

- It has an effect on the treatment of pathological conditions of the organism e.g. anemia.
- It has an effect on diseases of the digestive system e.g. chronic enteritis.
- It has increased diuretic properties.
- It does not burden the human body with calories as it has low lipid content and low calories.
- It helps to the prevention of atherosclerosis and hypertension.
- It has potential anticancer effects.
- It helps reduce high blood cholesterol.
- It has strong antioxidant and antimicrobial properties.
- It strengthens the immune system.

Maca Plant (*Lepidium meyenii*)

The Maca plant (*Lepidium meyenii*) is a turnip with several similarities to that of radish. It is a herbaceous biennial or annual plant that grows at high altitudes in South America. It has short stem and lace sheets that are renewed constantly. The seeds of the plant are the only way to reproduce and its yellow flowers are converted into fruits of the order of 4-5 millimeters. Scientific studies have highlighted the production of nutrients during the metabolism of a plurality of biologically active aromatic glycosinolates. The nutritional composition of maca plant is similar to that of cereals such as maize, rice, and wheat as it consists of 60-75%

carbohydrates, 10-14% proteins, 8.5% fiber and 2.2% lipids. One hundred g dry skin contains about 250 mg of calcium, 2 g potassium and 15 mg of iron as well as significant amounts of fatty acids and 0.05-0.1% sterols. It also contains vitamins B1, B2, B12, C and E, zinc, alkaloids, tannins and saponins.⁴ Plants' composition is essentially related to its contribution to sexual function and fertility, due to the high amino acid content. The high concentration in amino acids, such as phenylalanine, tyrosine and histidine, confer to the neurotransmitter constructing factor responsible for the neurotransmitter transmission of signals to the brain. The root of the plant is consumed fresh or dried or in the form of a capsule as a dietary supplement.⁴² According to literature maca plant consumption seems to have a number of benefits for human health, which are summarized at Table 10:^{2,42}

Cranberry (*Vaccinium oxycoccus*)

Cranberries (*Vaccinium oxycoccus*), is one type of red acidic berries which are fruits of small deciduous shrubs. Cranberries are mainly found in northern Europe and America. They are consumed fresh, dried, frozen as well as dietary supplements. They are very good source of nutrients and in particular 100 g of cranberries contain 13.30 mg of vitamin C, 4.60 g of fiber, 0.36 mg of manganese, 5.10 mg of vitamin K, and 1.20 mg of vitamin E, while having a very low calorie value. Cranberries are an excellent source of antioxidant ingredients, especially phenolic compounds and in particular they contain high concentrations of proanthocyanidins, flavonoids such as flavonols, quercetin and myricetin, ellagic

Table 10: Summary of some health benefits of maca plant

Health benefits	Compound/s responsible for benefits
improvement of sexual function and increased fertility	high amino acid content
Improving the symptoms of menopause antimicrobial and detoxifying action	Amino acids such as phenylalanine, tyrosine and histidine vitamins B1, B2, B12, C and E, zinc, alkaloids, tannins and saponins
Antidepressant action Supportive in endocrine system, adrenal glands and thyroid, while promoting regulation of metabolism	Amino acids such as phenylalanine, tyrosine and histidine vitamins B1, B2, B12, C and E, zinc, alkaloids, tannins and saponins

acid and chlorogenic acid. Hence they have the potential to provide strong protection against free radicals.⁴³ Research data on the potential beneficial effects of cranberries within the organization are focusing on the following axes:

Cardiovascular System

Studies have shown that consumption of cranberries may retard the progression of the atherosclerotic process to arteries and lower LDL cholesterol levels, hence reducing the risk of developing cardiovascular disease⁴³. Clinical and animal studies indicate that the consumption of cranberry juice decreases LDL and increases HDL cholesterol. Also, cranberry consumption improved lipidemic profile in mice fed a high fat diet.⁴⁴ Favorable effects of cranberry juice on blood lipids have been shown in the population, including obese men,⁴⁵ patients with diabetes mellitus⁴⁶ and patients with low HDL and hypertriglyceridemia.⁴⁷ Additionally, an in vitro study showed that cranberry extracts inhibit the conversion enzyme and, therefore, they reduce blood pressure.⁴⁸

Urinary System

Research evidence has shown that this superfood may contribute to prevention and treatment of urinary tract infections due to high antioxidant content components and in particular proanthocyanidins, which have stalling activity against bacteria such as *E. coli*.⁴³ In a meta-analysis,⁴⁹ with data from 10 studies with a total of 1,049 participants for a period of 12 months, results showed that the consumption of cranberry decreased the overall incidence of urinary tract infection by 35%, especially for women with recurrent urinary tract infections and have reduced the calvary annual percentage of new infections by 39%.³ Possible effect on cancer pathophysiology: Although the data is not yet clear, it seems that consumption of cranberry is likely to have little inhibitory effect on carcinogenesis and may contribute to the prevention of various forms of cancer such as breast, colon, prostate and lung cancer. This seems to be due to their ellagic acid content, antioxidant with strong action that prevents DNA alteration, but also other bioactive phytochemicals.

Other Actions

Consumption of cranberry seems to protect against the appearance of dental problems (gingivitis,

plaque, periodontitis etc.). Also, data show a potential impact on acceleration metabolism, the relief of skin diseases and the improvement of mood, through the effect on hormones.⁴³

Acai berries (*Euterpe oleracea*)

Acai berries are dark blue fruits and are fruits of a palm tree type with a height of 25 meters and 3-meter leaves, thriving in Amazon forest in Brazil. The acai berries are rich in ω -3 fatty acids, amino acids, proteins, electrolytes, metals, fibers, sterols, vitamins A, B1, C and E, iron, calcium, copper, magnesium, potassium and zinc. They contain in high amounts anthocyanins, which give them important antioxidant properties. The increased protein content, even higher than the egg, in combination with its important antioxidant properties make akai berry a superfood. One hundred (100) g of dried fruit purée of acai berries contain 8.1 g of protein, 52.2 g of carbohydrates, 32.5 g of fat, traces of vitamin C, 44.2 g of fiber, 260 mg of calcium, 4.4 mg of iron, 1002 IU vitamin A, glutamate and aspartic acid.^{50,51} Acai berries are consumed either raw or dried, while widely used as a dietary supplement in various forms. The scientific data suggests that eating acai berries within a balanced diet seems to offer significant benefits for the human organism. Consumption of this superfood seems to strengthen the human immune system, exerting intense antioxidant activity and preventing cell destruction by free radicals.⁵¹ They also provide to the human body fatty acids such as ω -3 and ω -9, which improve the lipidemic profile and exert anti-inflammatory action. Additionally, it appears that

Table 11: Summary of some health benefits of Acai berries

Health benefits	Compound/s responsible for benefits
strengthening the human immune system	anthocyanins
anti-inflammatory action	ω -3 and ω -9 fatty acids
protection against cancer cells	vitamins A, B1, C and E and anthocyanins

help human body by excretion of harmful toxins. The high content of acai berry in antioxidants was proven along with its multiple benefits for health. With the participation of 12 healthy volunteers, improvements to metabolic levels and protection against cancer cells were proven. Also after taking blood and urine samples at 12 and 24 hours from the consumption of acai berries juice, a high concentration of antioxidants, mainly anthocyanins, was observed in the blood.^{51,52} A summary of acai berries health benefits is presented at Table 11 below.

Goji berries (*Lycium barbarum*)

Goji berries are endemic fruits of Tibet. The fruits are easily oxidized, and they are almost never fresh, except in the production areas. The degree of drying is differentiated depending on the species. They also called "berries of happiness" with the scientific name *Lycium barbarum*. Goji berries are one of the richest natural sources of nutrients, such as -carotene, vitamins C, E, B1 and B2, minerals, antioxidants and amino acids. Also they contain a high percentage of carbohydrates, fatty acids and fibers. Goji's fruit contains 18 amino acids, 21 trace elements, such as zinc, calcium, germanium, selenium and phosphorus, vitamins of the B complex (B1, B2, B6), more beta-carotene than carrot, more iron from spinach, vitamin E, vitamin C at concentration 500 times higher than oranges,

phytosterols, such as beta-sitosterol and beneficial fatty acids such as linoleic acid.⁵³ Goji berries are superfood with multiple benefits within the human organism. The most important action documented by many studies, is the strong antioxidant protection against the harmful free radicals present in the human body. This has the consequence of being important contributing firstly to the prevention of diseases such as cardiovascular diseases and diabetes, the pathophysiology of which is promoted in the presence of free radicals, and secondly to the strengthening of the immune system. Another action of the goji berries being studied is the possible protection against cancer, although the data is not clear. The presence of polysaccharides in the form of glycosides appears to be associated with an effect on mechanisms of carcinogenesis, while the presence of germanium and various antioxidant substances enhance the potential protection against cardiovascular action. Concerning the effect on cardiovascular prevention goji berries contribute to the reduction of LDL and lowering of blood pressure. Additionally, consumption of goji berries has been associated with the enhancement of the endogenous antioxidant system, through increased production of enzymes such as superoxide dismutase, resulting in reduction of LDL oxidation. The contribution of goji berries to the proper regulation of blood sugar concentration and prevention of insulin resistance is scientifically recognized, since these are the key factors for the prevention of type II diabetes. Research data demonstrate the beneficial effects of goji berries and the enhancement of sexual function, by increasing testosterone levels.^{53,54} Goji berries can reduce inflammation, reduce blocking of the blood vessels, while they can contribute through the antioxidants contained in the prevention of various types of cancer. Goji contribute to improved vision due to its high content of antioxidants, including compounds such as zeaxanthin, lutein, polysaccharides and polyphenolic compounds. Beta-sitosterol of Goji berries seem to significantly inhibit stomach cancer, suppressing the reproduction of cells and toxicity production of cancer cells.⁵⁴ But there are not sufficient scientific data, but only indications hence further research for safer conclusions are needed. A summary of acai berries health benefits is presented at Table 12 below.

Table 12: Summary of some health benefits of Goji berries

Health benefits	Compound/s responsible for benefits
Prevention of cardiovascular diseases and diabetes	Polysaccharides in the form of glycosides, germanium and various antioxidant substances
Reduce of inflammation and blocking of the blood vessels	Antioxidants like phenolic compounds
Stomach Cancer prevention	Beta-sitosterol
Improve vision	Zeaxanthin, lutein, polysaccharides and polyphenolic compounds

Ginger Root (*Zingiber officinale*)

Ginger comes from South Asia with its cultivation now spreading to almost all tropical countries. It comes from a herbaceous plant of the family of *Zingiberaceae*, while it consists of a fleshy rhizome with dense branches. Mainly it consists of water (80%), while it contains satisfactory quantities of potassium, zinc and polyphenols. The nutritional value of ginger per 100 g is: 0.4 g fat, 18 g carbohydrate, 2 g fiber, 2 g protein, 43 mg magnesium, 2 mg copper, 415 mg potassium, 34 mg phosphorus, 16 mg calcium, sodium 13 mg, vitamin C 5 mg, folate 11 µg.⁵⁵ The main bioactivity and health benefits following ginger root consumption, as documented by various research studies, is presented below at Table 13.^{56,57}

Pomegranate (*Punica granatum L.*)

Pomegranates are the fruit of the plant *Punica Granatum L.*, which is a deciduous shrub 2-4 meters high or small tree of 5 to 7 m high. It is cultivated all over the world and thrives in light and cool soils, and multiplied during spring. The fruit of the pomegranate in most varieties consists of 24% bark, 14% of the spores and 62% of the juice. Pomegranate is considered a popular edible fruit, while in recent years a lot of scientific studies show potential beneficial effects of the pomegranate on health promotion and advocacy from various pathologies situations, hence scientists consider it as superfood. The important properties of the pomegranate are directly related to its high content of bioactive substances, including phenolic compounds, polyphenols, ellagitannins and vitamins. Many of these phytochemicals have been shown to have significant antioxidant and

anti-inflammatory properties which promote human health. The most important pomegranate polyphenol is punicalagin which is responsible for over 50% of the strong antioxidant activity of the juice. The high content of pomegranate in polyphenols seems to be associated with the prevention of hypertension and endothelial function improvement.^{58,59} Studies have shown that consumption of pomegranate juice can lead to improved arterial blood pressure, reduced triglyceride levels and increased HDL cholesterol. Therefore, and in combination with other data, there is evidence of a significant contribution of pomegranate to slowing the atherosclerotic procedure and reducing the risk of cardiovascular disease. Also, the punicic acid, which is found in the seeds of pomegranate, has been shown to inhibit the formation of prostaglandins. Generally, several studies have concluded that pomegranate juice consumption can be beneficial to high-risk populations of atherosclerotic and cardiovascular diseases, as well as people with high risk factor for diabetes. The high content of polyphenolic components, such as anthocyanins, ellagitannins, etc., can lead to improvement of cardiovascular biomarkers, provided that pomegranate is part of a balanced diet.⁶⁰ A summary of pomegranate health benefits is presented at Table 14.

Donkey Milk

Donkey milk seems to be the best substitute for human milk due to its content of lactose, proteins,

Table 14: Summary of some health benefits of pomegranate

Health benefits	Compound/s responsible for benefits	Compound/s responsible for benefits
Cardiovascular disease prevention	polyphenols	phenolic compounds especially punicalagin, polyphenols, ellagitannins and vitamins
Digestion	Inorganic compounds	Punicalagin
Antimicrobial and anti-inflammatory activity	Vitamin C, potassium, zinc and polyphenols	punicic acid, anthocyanins, ellagitannins

minerals and ω-3 fatty acids. In recent years, studies have highlighted its attributes and is considered as a superfood. The effect from colostrum and donkey milk (of the Martina Franca breed) in general has been evaluated on the functioning of the nerve cells of human peripheral blood (PBMC) to different intervals from lactation. The results showed that colostrum caused higher IgG responses, whereas donkey milk has triggered higher immunoglobulin G (IgG) responses, substances which are related to the strengthening of the immune system. Both the milk and colostrum had an effect on CD25 and CD69 of mononuclear cells that are related to the immune system via their involvement in T-cells. The ability of donkey milk to induce interleukins (IL) (IL-12, IL-1 beta and IL-10) release and tumor necrosis factor alpha (TNF α) was restricted to milk only, while colostrum lacks this ability. Finally, both colostrum as well as milk caused the release of nitric oxide (NO) with milk showing greater NO release activity, which promotes vasodilatation of the arterial endothelium. Taken together, these immunological effects are caused both from colostrum and donkey milk, can be useful in the prevention and / or treatment of human diseases associated with the immune system. Also, NO production from donkey milk can be very useful in preventing atherosclerosis, being a powerful vasodilator and an effective antimicrobial agent, as pathogens and / or their products play a strong proatherogenic role. Finally, donkey milk has been shown to have antimicrobial activity primarily against pathogenic microorganisms, hence protects against possible infections within the human body. However, more research is needed to strengthen data about the vigorous effects of donkey milk.^{61,62,63}

Summary of Superfood Properties

The Antioxidant Properties of Superfoods

Superfoods include a number of beneficial ingredients which the human organism is making use of, for the overall health improvement and the treatment of certain diseases. Superfoods when consumed even in small quantities are beneficial for the human body due to the number of beneficial substances contained. Some of the most important superfoods, such as kefir, maca plant, acai berries, goji berries, hippophaes, maize, blueberries, royal jelly, spirulina, ginger, donkey milk and pomegranate have become particularly important for the human health. Other superfoods that are reported in the literature are the aronia plant, quinoa, blackberry, and others. The most important benefit of superfoods has been shown to come from their high antioxidant content, such as carotenoids, vitamins A and E, and polyphenols. The creation of free radicals in the body is a result of normal biological processes, but the overproduction has a deleterious effect, destroying healthy cells speeding up the aging process and significantly increasing the likelihood of various diseases. At this point antioxidant components interfere and inhibit this process, scavenging the free radicals and inhibiting the resulting pathophysiological conditions associated with a variety of degeneration diseases. In a study conducted at the Department of chemistry at the National and Kapodistrian University of Athens (Proestos' unpublished work), the total antioxidant capacity (measured by the Ferric Reducing Antioxidant Power, FRAP assay) and total phenolic components (measured by Folin Ciocalteu method), after extraction with 50% aqueous methanol of various dried superfoods

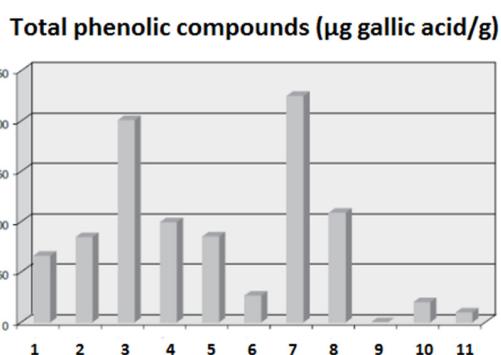


Fig. 1: Total phenolic compounds content (in µg gallic acid/g) of some superfoods, where:
1-cranberries, 2-aronia plant, 3-goji berries, 4-hippophaes, 5-blueberries, 6-quinoa, 7-raspberry,
8-acai berries, 9-ginger root fresh, 10-ginger root dried and 11-maca plant

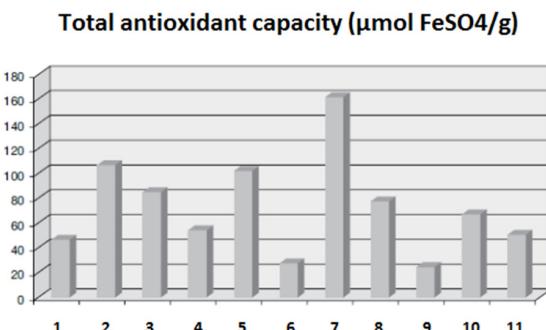


Fig. 2: Total antioxidant capacity (in $\mu\text{mol FeSO}_4/\text{g}$) of some superfoods, where: 1-cranberries, 2-aronia plant, 3-goji berries, 4-hippophae, 5-blueberries, 6-quinoa, 7-raspberry, 8-acai berries, 9-ginger root fresh, 10-ginger root dried and 11-maca plant.

was determined. The results showed high content of total phenolic compounds in goji berries, aronia plant, hippophae, blueberries, acai berries and raspberries, with goji berries and raspberry displaying the highest prices, which is explained by the high concentration of anthocyanins (Fig 1).

All of the above superfoods are rich in polyphenols, and in particular flavonoids, which have a high antioxidant activity. This also explains the high antioxidant activity observed in the same study for most of the superfoods with raspberries, aronia plant, blueberries and goji berries having the highest values (Figure 2).

The high antioxidant activity of superfoods is due to the high concentration of polyphenols on the one hand, and on the other the synergistic action of polyphenols with other antioxidants, such as carotenoids and vitamins A and E.

Superfoods within the Daily Diet

A review of the scientific data shows that superfood consumption can offer the human body a plethora of antimicrobial and antioxidant substances, fiber, plenty of vitamins (A, B, C, K, etc.), inorganic compounds but also beneficial fatty acids such as ω -3, ω -6 and other ingredients in quantities that often exceed the typical daily intake of other foods. The inclusion of superfoods in the daily diet can contribute to reduce the risk of various degenerative diseases, such as cardiovascular diseases, diabetes, metabolic syndrome, obesity, neurological conditions and cancer. So it seems that superfoods serve the basic role of conventional functional foods in

prevention, offering a high amount of bioactive compounds. At the same time, it is important that they provide a plethora of nutrients typically having low caloric content. Regardless of any recognized and scientifically documented health benefits of superfoods, it should be noted that a nutritional program should not be exclusively based in the presence of superfoods but these must be part of a healthy and balanced diet. However, continuous and fast rhythms of everyday life have led to the formation of a diet model in which certain foods which offer value nutrients are missing. This very "nutritional gap" can be covered by superfoods, by offering balanced nutrition on the one hand and significant health benefits on the other. That's the point where particular importance should be given to include superfoods in more and more nutritional standards, but not to replace the consumption of other foods that provide the human body with valuable nutrients. It is important, on the one hand, that consumers are informed by qualified scientific sources for those 'superfoods' for which there are sufficient evidence of their beneficial effects on human health to avoid the possibility of misleading, and on the other hand to understand that superfoods, which are more likely to be consumed as supplements, may have an adverse effect on their health (e.g. hypotension, pro-oxidative stress, removal from a balanced food, etc.). The continuous spread of superfoods is a fact due to the tendency to find new ways of shielding health, due to intense rhythms life of modern reality. In this context, superfoods when consumed stably and meticulously, preferably in the form of fresh or dried foodstuffs and only in special cases as supplements, always in the context of a balanced diet, can play an

important role in the direction of health promotion and the prevention of chronic diseases.

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Conflict of interest

The author declares no conflict of interest

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