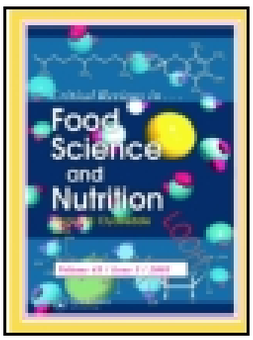

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REVIEW

The impact of rice bran oil consumption on the serum lipid profile in adults: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Dyslipidemia/hyperlipidemia is recognized among the risk factors for lifestyle related diseases. A healthy diet, rich in vegetable oils such as rice bran oil (RBO), may aid to improve serum lipid levels. Thus, the aim of this study was to assess the effects of rice bran oil (RBO) consumption on serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglyceride (TG) levels in adults. The following online databases were searched for manuscripts published until October 7th 2020: PubMed/Medline, Scopus, Clarivate Analytics' Web of Science, Cochrane Central Register of Controlled Trials, and Google Scholar. The effect sizes were expressed as weighted mean difference (WMD) with 95% confidence intervals (CI). A total of 8 eligible trials with 14 effect sizes were included in this meta-analysis. Our analysis revealed that the consumption of RBO significantly decreased serum TC (WMD: −7.29 mg/dL, 95% CI: −11.32, −3.25, P = 0.000), LDL-c (WMD: −7.62 mg/dL, 95% CI: −11.10, −4.14, P = 0.000) and TG (WMD: −9.19 mg/dL, 95% CI: −17.99, −0.38, P = 0.041) levels. So, available evidence suggests that RBO consumption can significantly decrease serum TC, LDL-c and TG levels. Hence, it may play a role in reducing dyslipidemia/hyperlipidemia risk.

KEYWORDS

HDL-c; LDL-c; meta-analysis; rice bran oil; systematic review; TC; TG; triacylglycerol

Highlights

- Due to its potential nutritional importance and health benefits, rice bran oil (RBO) has been suggested to influence the serum lipid profile.
- We reviewed the effects of RBO consumption on the lipid profile in adults.
- According to our findings, RBO consumption significantly decreases serum total cholesterol, low-density lipoprotein cholesterol and triglyceride levels.
- RBO had no significant effects on serum high-density lipoprotein cholesterol levels.

Introduction

Abnormal lipid metabolism is a condition that acknowledged as risk factor for life style related diseases. Lifestyle-related diseases, such as stroke, heart disease, and diabetes, are main examples of noncommunicable diseases and are now the major cause of death in the world (Aida et al. 2020). Dyslipidemia is a metabolic abnormality leading to an increase in plasma total cholesterol (TC) and triglycerides (TG) levels. It is described by elevated low-density lipoprotein cholesterol (LDL-C), also known as hypercholesterolemia, and often combined with low levels of high-density lipoprotein cholesterol (HDL-C) and elevated TG (Trautwein and McKay 2020). Lifestyle changes (e.g. dietary intervention) and medication are two crucial elements in the management of dyslipidemia. Changes in one's diet can reduce the need for medications and decrease their side effects (Ghobadi, Hassanzadeh-Rostami, Mohammadian, Zare, et al. 2019). In particular, oils, thanks to their composition, influence the hypercholesterolemia risk in a significant manner. Due to their richness in various fatty acid and exclusive ingredients, edible fats and oils can alter the lipid profile (Ghobadi, Hassanzadeh-Rostami, Mohammadian, Nikfetrat, et al. 2019). Recently, rice bran oil (RBO) has been regarded as a nutraceutical/functional food. This edible oil has been routinely consumed in several Asian countries, namely Japan, Korea, China, Taiwan and Thailand, and has also gained popularity on the Western markets due to its potential nutritional importance and health benefits. The composition of RBO exhibits a good balance between unsaturated fatty acids (FA) (oleic and linoleic) and saturated FA (palmitic). In addition, RBO contains a great variety of bioactive phytochemicals with confirmed nutritional benefits,

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e.g. γ-oryzanol (a mixture of ferulic acid esters of triterpene alcohols such as campesteryl ferulate, cycloartenyl ferulate and 24-methylenecycloartanyl ferulate) and vitamin E analogs, e.g. tocotrienols (α, ß, δ and especially γ-tocotrienol) and tocopherols (δ-tocopherol). What sets RBO apart from other vegetable oils available on the market is that it is the only source of γ-oryzanol, which has been reported to have an excellent nutritional functionality and is well-known to reduce plasma cholesterol (Tong and Jinsong 2019, Fujiwara 2019). Research conducted on animal models and in humans has concluded that RBO possesses considerable lipid-lowering effects. Noteworthy, experiments in which RBO or its unsaponifiable fractions (total tocopherols, γ-oryzanol, and squalene) were fed to animals have demonstrated that the unsaponifiable fractions of RBO are efficient in lowering circulating lipids levels and the aortic accumulation of cholesterol esters (Rukmini and Raghuram 1991, Friedman 2013). However, studies conducted on human subjects have produced contradictory results. To our knowledge, so far only one meta-analysis has investigated the effects of RBO consumption on the lipid profile in humans. The aforementioned study, conducted by Jolfaie et al.(Jolfaie et al. 2016), provided contradicting results and was limited by several flaws. Moreover, since it was conducted in 2015, data published from 2015 until now has not been evaluated. Consequently, we decided to conduct a systematic review and meta-analysis to study the effect of RBO consumption on the lipid profile in human adults.

Methods

The current systematic review and meta-analysis was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2015) in terms of processing, analyzing, and reporting of the data.

Search strategy

The PubMed/Medline, Scopus, Clarivate Analytics' Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar online databases were searched until October 7th 2020 to find appropriate studies published before this date, without language, time or any other limitations. The type of article was restricted to randomized controlled trials (RCTs) or clinical trials. We used the following keywords: ((cholesterol*) OR (LDL*) OR (TC) OR (HDL*) OR (triglyceride*) OR (TG) OR (lipoprotein*) OR ("lipid profile") OR (Lipid*) OR ("cardiovascular disease") OR ("heart disease") OR (hypercholesterolemia*)) AND ((rice oil*) OR ("rice bran*") OR ("rice bran oil") OR ("rice germ oil") OR ("rice bran extract") OR ("oryza sativa oil*") OR ("oryza sativa bran*")) NOT ((rat) OR (mouse) OR (vitro*) OR (animal*))

Study selection and eligibility criteria

Two independent researchers (B.P. & S.F.) performed the screening of the titles and abstracts and the further assessment of the full-texts of the qualified articles. All the published controlled clinical trials (either with a parallel or a cross-over design) that reported the results of RBO consumption on the serum lipids (TC, LDL-c, HDL-c or TG) in adults (subjects aged ≥18 years) were considered. A specific time frame was not considered for the search and we reviewed all the studies conducted on this topic until October 2020. The exclusion criteria were: 1) animal and in vitro studies; 2) studies conducted on children, including adolescents; 3) studies which examined the effect of RBO in combination with other oils; 4) studies that investigated rice bran, rice bran powder, rice bran fiber, and rice bran fortified foods; 5) studies that examined only certain compounds of the RBO, such as γ-oryzanol, vitamin E (α-, β-, γ-, and δ-tocopherols and tocotrienols) or ferulic acid; 6) studies have examined RBO together with a specific dietary pattern; 7) studies comparing RBO with brown RBO; 8) studies that examined rice bran extract that was not RBO; 9) studies that evaluated margarine fortified with specific compounds or sterols in RBO; 10) studies comparing RBO with rice bran powder; 11) studies in which the control group was another oil; 12) studies in which the duration of the intervention was <2 weeks; 13) studies without complete information or without a control group; 14) unrelated or inaccessible studies; 15) studies which evaluated other elements rather than the lipid profile; 16) studies in which the results were reported in the form of illegible graphs; 17) studies with duplicate data found in another study; and 18) articles with other study designs except for a clinical trial design.

Data extraction

Two independent researchers (B.P.) and (M.H.S.) selected the studies based on the inclusion and exclusion criteria. Any discrepancy between the researchers was solved by consulting with a third researcher (F.S.H.). The following information was collected: author's name, year of publication, study location, clinical trial design, study population, mean age, sex, sample size, intervention group, control group, RBO dosage, control oil dosage, and duration of intervention. This information is presented in Table 1.

Quality assessment

The quality of the studies was independently assessed by 2 researchers (B.P.) and (F.S.H.) according to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (Higgins 2008) and by evaluating the following criteria: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, and 6) selective outcome reporting. There were six key areas according to which each study was rated in terms of the overall risk of bias: low-risk (low for all key areas), high-risk (high for one

Table 1. Characteristics of the randomized clinical trials that were included in the systematic review.

	Author (year)	study location	Clinical Trial Design	Population	Mean Age (year)	Sex	Sample Size Case/ Control	Intervention group	Control group	Rice bran oil dosage (geram/day)	Control oil dosage (geram/day)	duration of intervention (week)
1	(Chen and Tsai 1995)	Taiwan	cross over clinical trial	Healthy	24	Male	10/10	RBO	soybean oil	NR	NR	2.5
2	(Chen and Tsai 1995)	Taiwan	cross over clinical trial	Healthy	24	Male	10/10	RBO	olive oil	NR	NR	2.5
3	(Chen and Tsai 1995)	Taiwan	cross over clinical trial	Healthy	24	Male	10/10	RBO	liquid lard	NR	NR	2.5
4	(Eady et al. 2011)	New Zealand	randomized, double-blind, cross-over trial	Hypercholesterolemic	51.5	Both sexes	39/39	RBOS	SS	20	NR	4
5	(Eady et al. 2011)	New Zealand	randomized, double-blind, cross-over trial	Hypercholesterolemic	52.8	Both sexes	36/36	RBO	sunflower oil	47.6	27.6	4
6	(Kuriyan et al. 2005)	India	Randomized cross-over clinical trial	Hypercholesterolemic	50	Both sexes	14/14	RBO	refined sunflower oil	NR	NR	13
7	(Lai et al. 2011)	Taiwan	randomized single blind placebo comparison study	Type 2 Diabetes	56.8	NR	17/18	RBO	soybean oil	18	18	5
8	(Lichtenstein et al. 1994)	*United States*	randomized, double-blind, cross-over trial	Hypercholesterolemic	61	Both sexes	15/15	RBO	corn oil	NR	NR	4.5
9	(Lichtenstein et al. 1994)	*United States*	randomized, double-blind, cross-over trial	Hypercholesterolemic	61	Both sexes	15/15	RBO	Canola oil	NR	NR	4.5
10	(Lichtenstein et al. 1994)	*United States*	randomized, double-blind, cross-over trial	Hypercholesterolemic	61	Both sexes	15/15	RBO	olive oil	NR	NR	4.5
11	(Most et al. 2005)	*United States*	randomized, double-blind, cross-over trial	Healthy	33.6	Both sexes	14/14	RBO	oil blend composed of peanut oil, olive oil, corn oil, canola oil, palm oil, butter	NR	NR	5
12	(Salar, Faghih, and Pishdad 2016)	Iran	single-center, randomized, controlled, parallel-group trial	Type 2 Diabetes	51	Female	25/23	RBO	sunflower oil	30	30	8
13	(Salar, Faghih, and Pishdad 2016)	Iran	single-center, randomized, controlled, parallel-group trial	Type 2 Diabetes	51.1	Female	25/24	RBO	Canola oil	30	30	8
14	(Wijayanthie, Gunarti, and Manikam 2019)	Indonesia	randomized, single-blind, crossover clinical trial	Type 2 Diabetes	48.9	Both sexes	10/10	RBO	virgin olive oil	13.8	13.8	4

NR: not report, RBO: Rice Bran Oil, RBOS: Rice Bran Oil Spread, SS: standard sprea

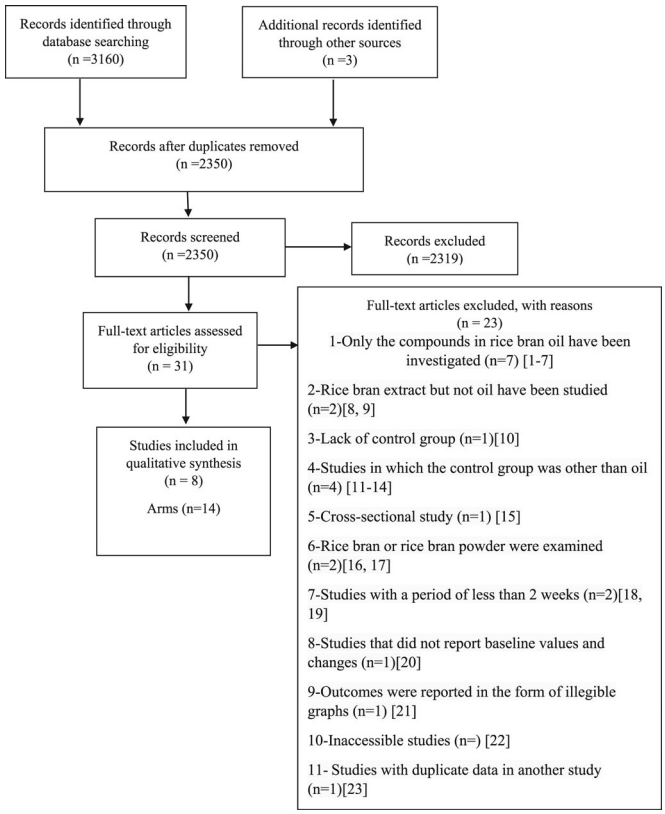

Figure 1. Flow chart of the study selection process.

or more key area) and unclear risk (unclear for one or more key area).

Data synthesis and statistical analysis

For all effects, the effect sizes were determined by the mean difference between the intervention and the control group at follow-up. Where the effect size was not stated, the difference in the mean values at the baseline and at the end of the study were used. We elicited the mean and the standard deviation (SD) from the reviewed studies and where the data were described in a different format. This technique was used by Hozo et al. as follows: SD = square root [(SD pretreatment) 2 + (SD post-treatment) 2 – (2 R × SD pretreatment × SD post-treatment)] (Hozo, Djulbegovic, and Hozo 2005). The random effects model (DerSimonian and Laird method) was used in order to evaluate the effect sizes and the results were provided across weighted mean difference (WMD) and 95% confidence intervals (CI). We used the Plot digitizer software when the results only existed in the graphic form. Heterogeneity was calculated by the I^2 index (Fatahi et al. 2018). We considered an I^2 index greater than 50% as an index of significant heterogeneity among the studies. Subgroup analysis was conducted to recognize factors for high heterogeneity. We considered the values less or more than the median as the cutoff values for each above mentioned quantitative parameter of subgroups. The sensitivity analysis was done by utilizing the leave-one-out method to measure the impact of each study on the results. We used the funnel plot to determine publication bias by either Begg's rank correlation or Eggers' regression test. STATA version 11.0 was used for statistical analysis (Stata Corp, College Station, TX) and we considered P-values <0.05 statistically significant.

Results

Study selection

A flow chart describing the literature search and the selection is presented in Figure 1. Using the key terms of the study, we identified 3160 articles through searching the databases and three additional articles through other sources. Firstly, duplicate articles (n = 813) were removed and then another 2319 articles, approved to be irrelevant, were removed after reading their titles and abstracts. Next, we assessed the full-texts of the remaining 31 articles of which 23 articles were excluded for the subsequent reasons: 1. only the compounds in RBO have been investigated and not RBO itself (n = 7) (Berger et al. 2005b, Ishihara 1984, Kerckhoffs et al. 2000, Qureshi et al. 1997, Vissers et al. 2000, Weststrate and Meijer 1998, Bumrungpert et al. 2019); 2. rice bran extract but not RBO has been studied (n = 2) (Ito, Nakashima, and Matsuoka 2015, Nhung et al. 2016); 3. lack of a control group (n = 1) (Rajnarayana, Prabhakar, and Krishna 2001); 4. the control group was another compound rather than an oil (n = 4) (Calvo-Castro et al. 2019, Kustiyah et al. 2019, Shakib, Gabrial, and Gabrial 2014, Zavoshy, Mostafa, and Hassan 2012); 5. the study design was cross-sectional (n = 1) (Maurya, Arya, and Sengar 2020); 6. rice bran or rice bran powder were examined (n = 2) (Murata et al. 2007, Sanders and Reddy 1992); 7. the period of the study was <2 weeks (n = 2) (Oshima, Suzuki, and Imai 1972, Suzuki and Oshima 1970); 8. the study did not report the baseline values and changes (n = 1) (Utarwuthipong et al. 2009); 9. the outcomes were reported in the form of illegible graphs (n = 1) (Tan et al. 2017); 11. the studies were inaccessible (n=) (Raghuram, Brahmaji Rao, and Rukmini 1989); and 12. the study data were reported as a duplicate from another study (n = 1) (Schwab et al. 1998). In the study by Bumrungpert et al.(Bumrungpert et al. 2019), three different doses of γ-oryzanol in RBO were compared with soybean oil. Since most of the studies included in the present meta-analysis did not report the dose of γ-oryzanol, it was not possible to perform a subgroup analysis based on the γ-oryzanol dosage and consequently this study was omitted. On the other hand, in research of Berger et al. (Berger et al. 2005b), peanut oil was administered to patients for 2 weeks in the run-in period and then two different doses of γ-oryzanol were compared to 4 weeks. Therefore, this study was also omitted. Schwab et al.(Schwab et al. 1998) reported duplicate data from the study of Lichtenstein et al. (Lichtenstein et al. 1994) and since their only new report was the comparison of RBO with beef tallow which is not a liquid oil (the type and physical form of the beef tallow was not reported), it was not entered into the analysis. The two reviewers (B.P.) and (F.S.H.) approved the study screening procedure. Although we finally selected eight articles for the analysis, some of them can be viewed as separate trials because, in

these studies, RBO was compared to more than one type of oil (Salar, Faghih, and Pishdad 2016, Lichtenstein et al. 1994, Eady et al. 2011, Chen and Tsai 1995). Therefore, we included eight articles in this systematic review with the effect sizes of 14.

Study and participant characteristics

The characteristics of the studies included in the present systematic review and meta-analysis are displayed in Table 1. Two studies were conducted in Taiwan (Chen and Tsai 1995, Lai et al. 2011), two in the United States (Most et al. 2005, Lichtenstein et al. 1994) and the others were conducted in New Zealand, India, Iran and Indonesia. From the total of 8 articles, two studies were parallel in design (Lai et al. 2011, Salar, Faghih, and Pishdad 2016) and the others were cross-over in design. Three studies were double-blinded (Eady et al. 2011, Lichtenstein et al. 1994, Most et al. 2005) with 65 participants and two studies (Lai et al. 2011, Wijayanthie, Gunarti, and Manikam 2019) with 45 participants were single-blinded. The intervention duration was 2.5 weeks in one study (Chen and Tsai 1995), 4 weeks in two studies (Eady et al. 2011, Wijayanthie, Gunarti, and Manikam 2019), 4.5 weeks in one study (Lichtenstein et al. 1994), 5 weeks in two studies (Lai et al. 2011, Most et al. 2005), 8 weeks in one study (Salar, Faghih, and Pishdad 2016) and 13 weeks in one study (Kuriyan et al. 2005). Among these studies, two had examined the effects of RBO in healthy subjects (Chen and Tsai 1995, Most et al. 2005), three in hypercholesterolemic subjects (Eady et al. 2011, Kuriyan et al. 2005, Lichtenstein et al. 1994) and three in patients with type 2 diabetes mellitus (Salar, Faghih, and Pishdad 2016, Wijayanthie, Gunarti, and Manikam 2019, Lai et al. 2011). One study did not report the gender of the participants (Lai et al. 2011), five studies included both males and females (Lichtenstein et al. 1994, Eady et al. 2011, Kuriyan et al. 2005, Wijayanthie, Gunarti, and Manikam 2019, Most et al. 2005), one study only involved adult females (Salar, Faghih, and Pishdad 2016) and one was only conducted on adult males (Chen and Tsai 1995). Overall, the age range of the participants was 24-61 years. In 7 of the 14 effect sizes, the control group received oil containing a higher amount of MUFA than PUFA and SFA, i.e. olive oil (Chen and Tsai 1995, Lichtenstein et al. 1994), virgin olive oil (Wijayanthie, Gunarti, and Manikam 2019), liquid lard (Chen and Tsai 1995), canola oil (Lichtenstein et al. 1994, Salar, Faghih, and Pishdad 2016) and oil blend composed of peanut oil, olive oil, corn oil, canola oil, palm oil and butter (Most et al. 2005), while in the other 7 effect sizes, the control group received oil containing a higher amount of PUFA than MUFA and SFA, i.e. soybean oil (Chen and Tsai 1995, Lai et al. 2011), sunflower oil (Eady et al. 2011, Kuriyan et al. 2005, Salar, Faghih, and Pishdad 2016), corn oil (Lichtenstein et al. 1994) and standard oil spread (Eady et al. 2011). In all the studies, the individual food and calorie intakes were checked, while 7 studies did not mention the use of a physical activity questionnaire, except for one study which mentioned this issue (Kuriyan et al. 2005). The run-in period was only mentioned in 4 studies (Chen and Tsai 1995, Eady et al. 2011, Lichtenstein et al. 1994, Salar, Faghih, and Pishdad 2016). Participants did not take cholesterol-lowering medication in all the studies except for one (Lai et al. 2011) in which this aspect was not mentioned. In none of the studies, the type of intervention was not different in the intervention and control groups, except for the oil consumed.

Risk of bias assessment

As shown in Table 3, except for two studies (Eady et al. 2011, Salar, Faghih, and Pishdad 2016) that were considered as having a low risk of bias in the random sequence generation, the other studies did not explicitly mention the randomization or random sequence generation methods. Therefore, they were regarded as having an unclear risk of bias. All the studies were assessed as having an unclear risk of bias in the allocation concealment because they did not mention the concealment or the method employed to perform this operation. There were three studies (Eady et al. 2011, Lichtenstein et al. 1994, Most et al. 2005) which were double-blind randomized controlled trials (RCTs) and were thus considered as having a low risk of bias for the blinding of the participants and personnel. There were also two studies designed as single blind trials (Lai et al. 2011, Wijayanthie, Gunarti, and Manikam 2019) which were therefore considered as having an unclear risk of bias. None of the trials provided a clear explanation of the blinding of the outcome assessment and other issues. Three studies (Lichtenstein et al. 1994, Most et al. 2005, Kuriyan et al. 2005) were clear in providing incomplete outcome data and the other five articles were not clear on this matter. Three studies were assessed as having an unclear risk of bias in the selective reporting (Chen and Tsai 1995, Eady et al. 2011, Most et al. 2005), and the other five studies as having a low risk of bias. Since all the studies were considered as having an unclear risk of bias for at least one of the six key domains, we found the quality of these studies "unclear".

Meta-analysis

A total of 14 studies with 270 participants (case = 205, and control = 203) which reported TC, LDL-c, HDL-c and TG as outcome measures, were included in the meta-analysis (Figure 2). Also, the results of subgroup analysis are shown in Table 2 and Supplementary Figures.

Total cholesterol (TC)

The combined results of the random-effects model displayed a significant decrease in TC following RBO consumption (weight mean difference (WMD): −7.29 mg/dL, 95% CI: −11.32, −3.25, P = 0.000) without a significant heterogeneity among the studies (I^2=37.3%, P = 0.078) (Figure 2a). The subgroup analysis for BMI showed that the reduction of TC was significantly higher in the overweight subjects (BMI: 25-29.9 kg/m^2) (WMD= −8.04; 95% CI:-14.45, −1.64)

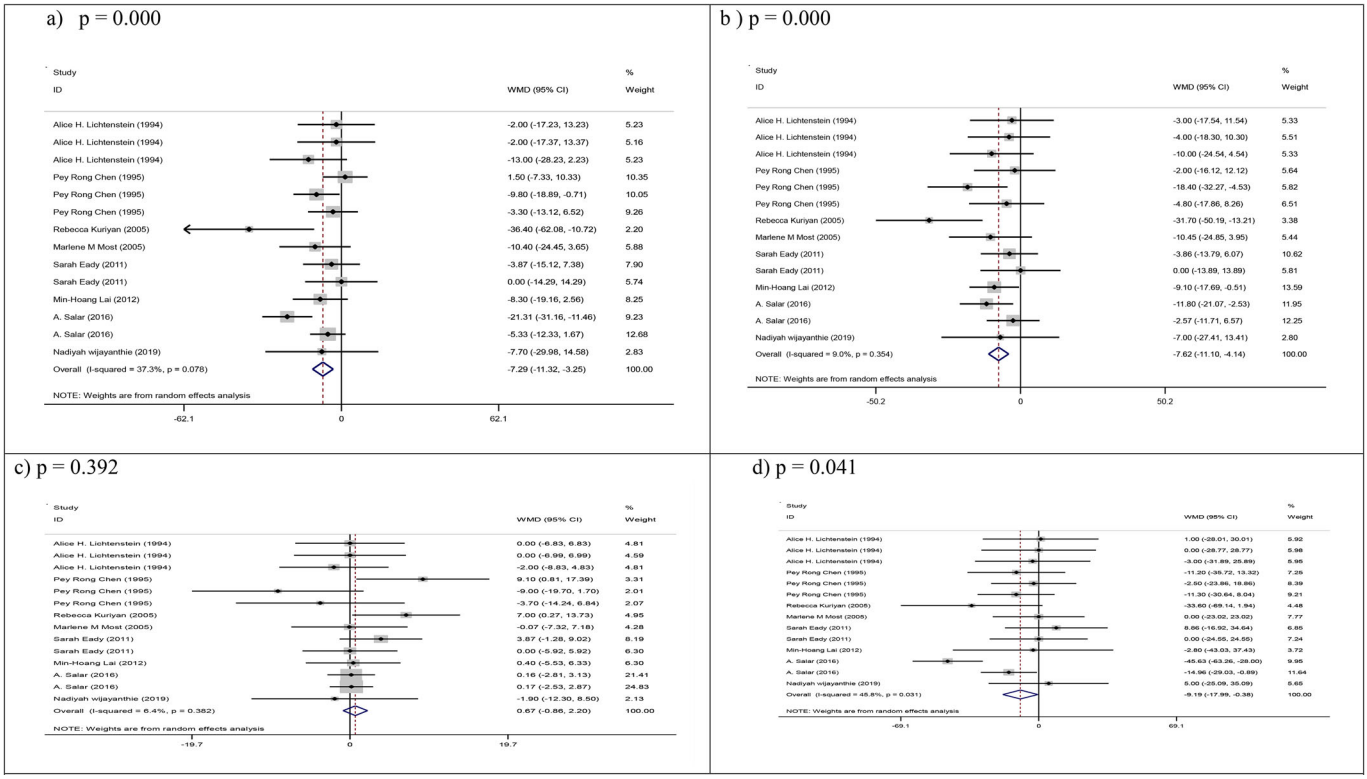

Figure 2. Forest plots from the meta-analysis of clinical trials investigating the effects of rice bran oil on (a) total cholesterol, (b) LDL-c, (c) HDL-c, and d) TG.

compared to those with a normal weight (BMI: 18-24.9 kg/m^2) (Supplementary Figure 1a). In addition, the reduction of TC was significantly higher in subjects ≥ 50 years old (WMD= −8.72; 95% CI:-14.53, −2.92) (Supplementary Figure 1b) and when the duration of the intervention was ≥ 5 weeks (WMD= −13.26; 95% CI:-21.77, −4.75) (Supplementary Figure 1c). Moreover, TC reduction was significant when the oils used contained a higher amount of MUFA *versus* (WMD= −6.74; 95% CI:-10.87, −2.61) (Supplementary Figure 1d). The sensitivity analysis indicated that no study had a significant impact on the overall effect sizes of TC (Supplementary Figure 5a). The assessment of the publication bias by the visual inspection of the funnel plot did not show any evidence of publication bias in the meta-analysis evaluating the effects of RBO on TC (P = 0.476) (Supplementary Figure 6a).

Low-density lipoprotein cholesterol (LDL-c)

The combined results of the random-effects model showed a significant reduction in LDL-c following RBO consumption (WMD: −7.62 mg/dL, 95% CI: −11.10, −4.14, P = 0.000) without a significant heterogeneity among the studies (I^2=9.0%, P = 0.354) (Figure 2b). The subgroup analysis for BMI displayed that the reduction of LDL-c was significantly higher in participants with a normal weight (WMD= −10.45; 95% CI:-18.30, −2.61) compared to those diagnosed with overweight (WMD= −5.84; 95% CI:-10.53, −1.15) (Supplementary Figure 2a). In addition, the reduction in LDL-c was significantly higher in subjects <50 years old (WMD= −8.63; 95% CI:-15.18, −2.08) (Supplementary Figure 2b) and when the duration of the intervention lasted ≥ 5 weeks (WMD= −10.76; 95% CI:-17.78, −3.76) (Supplementary Figure 2c). The sensitivity analysis showed that no study had a significant effect on the overall effect sizes of LDL-c (Supplementary Figure 5b), and the evaluation of the publication bias by the visual inspection of the funnel plot did not show any evidence of publication bias in the meta-analysis evaluating the effects of RBO on LDL-c (P = 0.411) (Supplementary Figure 6b).

High-density lipoprotein cholesterol (HDL-c)

The combined results of the random-effects model showed no significant increase in HDL-c following RBO consumption (WMD: 0.67 mg/dL, 95% CI: −0.86, 2.20, P = 0.392) and no significant heterogeneity among the studies (I^2=6.4%, P = 0.382) (Figure 2c). The sensitivity analysis revealed that no study had a significant impact on the overall effect sizes of HDL-c (Supplementary Figure 5c). The assessment of the publication bias by the visual inspection of the funnel plot did not display any evidence of publication bias in the meta-analysis of RBO consumption on HDL-c (P = 0.351) (Supplementary Figure 6c).

Triglycerides (TG)

The combined results of the random-effects model showed a significant reduction in TG following RBO consumption (WMD: −9.19 mg/dL, 95% CI: −17.99, −0.38, P = 0.041) with relatively high heterogeneity among the studies

Table 2. Subgroup analyses for TC, LDL-c, HDL-c and TG based on BMI, age, duration of intervention and type of control (MUFA/PUFA rich oils).

Subgroups	No.	I^2 (%)	p-heterogeneity intergroup	WMD(95% CI)	$P_{between}$
Total cholesterol		37.3	0.078		
BMI					0.09
Normal	6	47.8	0.088	−6.52 (-13.04, 0.00)	
Overweight or obese	7	42.1	0.110	−8.04 (-14.45, −1.64)	
NR	1	–	–	−8.30 (-19.16, 2.56)	
Age					0.35
< 50 years old	5	0.0	0.422	−4.76 (-9.62, 0.10)	
≥ 50 years old	9	48.5	0.049	−8.72 (-14.53, −2.92)	
Duration of intervention					0.56
< 5 weeks	9	0.0	0.762	−4.01 (-8.00, −0.03)	
≥ 5 weeks	5	62.7	0.030	−13.26 (-21.77, −4.75)	
Type of control (MUFA/PUFA rich oils)					0.69
PUFA	7	67.3	0.005	−8.13 (-16.34, 0.09)	
MUFA	7	0	0.885	−6.74 (-10.87, −2.61)	
LDL-c		9.0	0.354		
BMI					0.61
Normal	6	49.7	0.077	−10.45 (-18.30, −2.61)	
Overweight or obese	7	0.0	0.771	−5.84 (-10.53, −1.15)	
NR	1	–	–	−9.10 (-17.69, −0.51)	
Age					0.47
<50 years old	5	0.0	0.530	−8.63 (-15.18, −2.08)	
≥50 years old	9	27.1	0.203	−7.34 (-11.91, −2.78)	
Duration of intervention					0.59
< 5 weeks	9	0.0	0.777	−5.62 (-10.18, −1.07)	
≥ 5 weeks	5	50.0	0.092	−10.78 (-17.79, −3.76)	
Type of control (MUFA/PUFA rich oils)					0.44
PUFA	7	40.6	0.121	−7.86 (-13.71, −2.00)	
MUFA	7	0.0	0.656	−7.24 (-12.24, −2.23)	
HDL-c		6.4	0.382		
BMI					0.82
Normal	6	52.9	0.060	2.17 (-2.42, 6.75)	
Overweight or obese	7	0.0	0.998	−0.05 (-1.74, 1.63)	
NR	1	–	–	0.40 (-5.53, 6.33)	
Age					0.48
<50 years old	5	49.7	0.094	−0.52 (-6.36, 5.33)	
≥50 years old	9	0.0	0.665	0.72 (-0.8, 2.25)	
Duration of intervention					0.36
< 5 weeks	9	21.5	0.252	0.43 (-2.36, 3.23)	
≥ 5 weeks	5	0.0	0.449	0.64 (-1.12, 2.41)	
Type of control (MUFA/PUFA rich oils)					0.67
PUFA	7	24.0	0.246	2.09 (-0.28, 4.47)	
MUFA	7	0.0	0.773	−0.67 (-2.78, 1.44)	
TG		45.8	0.031		
BMI					0.05
Normal	6	0.0	0.491	−6.31 (-15.97, 3.35)	
Overweight or obese	7	65.9	0.007	−10.45 (-25.55, 4.66)	
NR	1	–	–	−2.80 (-43.03, 37.43)	
Age					0.06
<50 years old	5	0.0	0.860	−5.13 (-15.37, 5.12)	
≥50 years old	9	61.2	0.008	−11.24 (-24.68, 2.19)	
Duration of intervention					0.09
< 5 weeks	9	0.0	0.967	−2.63 (-10.97, 5.70)	
≥ 5 weeks	5	68.4	0.013	−20.52 (-38.98, −2.05)	
Type of control (MUFA/PUFA rich oils)					0.04
PUFA	7	68.2	0.004	−12.72 (-30.65, 5.22)	
MUFA	7	0.0	0.827	−7.14 (-15.22, 0.94)	

WMD, weighted mean difference; BMI, body mass index; NR, no reported; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; LDL-c, low density lipoprotein-cholesterol; HDL-c, high density lipoprotein-cholesterol; TG, Triglyceride

(I^2=45.8%, P = 0.031) (Figure 2d). BMI, age, duration of intervention and type of control were considered as possible sources of heterogeneity. The subgroup analysis indicated that the reduction of TG was significantly higher if the duration of intervention was ≥ 5 weeks (WMD= −20.52; 95% CI:-38.98, −2.05) compared to <5 weeks (Supplementary Figure 4c). The sensitivity analysis showed that no study had a significant impact on the overall effect sizes of TG (Supplementary Figure 5d), and the assessment of the publication bias by the visual inspection of the funnel plot did not demonstrate any evidence of publication bias in the meta-analysis of the effect of RBO consumption on TG (P = 0.324) (Supplementary Figure 6d).

Discussion

This systematic review and meta-analysis evaluated eight clinical controlled trials which had examined the effects of RBO on the serum lipid profiles in adults. The results of our analyzes showed that serum TC, LDL-c and TG levels significantly decreased in the group receiving RBO as

Table 3. Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool.

Study, Year (reference)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall assessment of risk of bias
(Chen and Tsai 1995)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(Eady et al. 2011)	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear
(Kuriyan et al. 2005)	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
(Lai et al. 2011)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
(Lichtenstein et al. 1994)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
(Most et al. 2005)	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
(Salar, Faghih, and Pishdad 2016)	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
(Wijayanthie, Gunarti, and Manikam 2019)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear

Table 4. Types of control oils based on their richness in fatty acids.

Oil	Rich in SFA	Rich in PUFA	Rich in MUFA
Soybean oil		✓	
Olive oil			✓
Virgin olive oil			✓
Canola oil			✓
Sunflower oil		✓	
Corn oil		✓	
Liquid lard			✓
Palm oil			✓
standard oil spread (SS)		✓	
Oil blend composed of peanut oil, olive oil, corn oil,canola oil, palm oil, butter			✓

compared to the control group. However, the effect of RBO on HDL-c was not statistically significant. Considering the association between RBO and serum TC, LDL-c, and HDL-c, our findings are similar to the previous meta-analysis that has been done in this area, but in the case of TG, the results are different. A previously conducted meta-analysis by Jolfaie et al. (Jolfaie et al. 2016) has reported reductions in TC (-12.65 mg/dL, 95% CI: −18.04, −7.27, $P < 0.001$) and LDL-c (-6.91 mg/dL, 95% CI: −10.24, −3.57, $P < 0.001$) levels after the consumption of RBO, but no significant effect was observed on serum HDL-c (0.74 mg/dL, 95% CI: −0.57, 2.05, $P = 0.27$) and TG levels (-11.67 mg/dL, 95% CI: −26.68, 3.33, $P = 0.127$). Noteworthy, the aforementioned study is inconsistent for several reasons: 1. Different control groups were compared to RBO, meaning that both the oil consumption control groups and the control groups that were not given a specific oil and only had a low calorie diet or weight maintenance diet, were analyzed together without any subgroup analysis in this regard, 2. The absence of subgroup analyses based on different oils that were included in the meta-analysis as a control group, on their similarities, e.g. the content in fatty acids, in order to understand better the effects of RBO on the lipid profile, 3. Two of the studies that were included in the meta-analysis only examined specific compounds in RBO, not RBO itself (Berger et al. 2005b, Vissers et al. 2000), 4. One of the studies included in the meta-analysis (Lichtenstein et al. 1994) had more than one effect size, due to the comparison of RBO with more than one oil, and only one of these effect sizes were mentioned in the meta-analysis, 5. A study dating back to 1995 and conducted by Chen et al. (Chen and Tsai 1995) was not included in the meta-analysis, 6. The studies of Rajanarayana et al. (Rajnarayana, Prabhakar, and Krishna 2001) and Utarwuthipong et al. (Utarwuthipong et al. 2009), which were mentioned in the meta-analysis, did not report the control group and changes values, respectively. Finally, since this study was conducted in 2015, it is certain that related articles published after this date were not included in the meta-analysis. Therefore, these reasons might account for the observed differences in the results, namely the effect of RBO on TG levels.

The fatty acid composition of RBO is very similar to peanut oil, however peanut oil has little cholesterol-lowering effects as compared to RBO (Berger et al. 2005a, Trautwein and McKay 2020). Thus, the beneficial properties of RBO on TC and LDL-c are probably related to its richness in non-saponifiable compounds, namely sterols, γ-oryzanol, and tocotrienols. Lichtenstien et al. (Lichtenstein et al. 1994) showed that RBO has the highest concentration of β-sitosterol, campesterol and stigmasterol *versus* canola, olive or corn oil. Sterols and cholesterol compete for absorption from the mixed micelles in the gut due to their structural similarities (Moreau, Whitaker, and Hicks 2002). Considering their higher affinity for micelles (Armstrong and Carey 1987), plant sterols are responsible for a 30-40% decrease in the cholesterol absorption (Ostlund 2007). On the other hand, γ-oryzanol and tocotrienols in RBO decrease the rate of endogenous synthesis of cholesterol by inhibiting the HMG-CoA reductase enzyme (Minhajuddin, Beg, and Iqbal 2005, Wang et al. 2015). Furthermore, the consumption of RBO increases the gene expression of cholesterol 7-alpha-hydroxylase (CYP7A1), which is the rate-limiting enzyme in the synthesis of bile acids from cholesterol. Therefore, a higher amount of cholesterol is eliminated from the body in the form of bile acids. Moreover, RBO elevates the hepatic gene expression of the LDL-receptor, resulting in an elevated cholesterol uptake from the blood into the liver (Chen and Cheng 2006). According to our results, RBO reduces TC in a higher extent when the control group consumed oils rich in MUFA *versus* PUFA. It seems that, due to the cholesterol-lowering effects of PUFA

(Abdelhamid et al. 2018, Hooper et al. 2015), the differences in TC between RBO consumption and high-PUFA oils consumption are insignificant. Unexpectedly, the subgroup analysis results showed that the reduction of LDL-c was significantly higher in participants with a normal weight compared to those with overweight. A study by Kuryan et al. which was conducted on normal-weight hypercholesterolemic patients has a major contribution to this finding. Since this population had higher serum levels of LDL-c, the observed effects of RBO were more significant. In addition, the impressive reduction of LDL-c in this trial may have been related to the long duration of the intervention (13 weeks) (Kuriyan et al. 2005).

Previous animal and human studies have reported that the prescription of RBO can reduce serum TG levels (Purushothama, Raina, and Hariharan 1995, Salar, Faghih, and Pishdad 2016). The omega-3 fatty acids content of RBO can inhibit the apolipoprotein-B100 and VLDL-C synthesis and consequently cause a reduction in TG levels (Harris, Dayspring, and Moran 2013, Lichtenstein et al. 1994). The induction of the lipoprotein lipase by RBO is another suggested mechanism responsible for the decrease in TG levels (Salar, Faghih, and Pishdad 2016), however the exact mechanism remains unclear.

The present study has some strengths. Firstly, we applied no time or language restrictions as inclusion criteria for the studies that evaluated the effects of RBO on the lipid profile. Secondly, due to the fact that the oils employed as controls differed in the studies, in order to reduce the bias related to the inequality of the control groups, we divided the control oils into two categories, namely rich in MUFA and rich in PUFA (Table 4) (Fujiwara 2019, Chen and Tsai 1995, Eady et al. 2011, Lai et al. 2011, Lichtenstein et al. 1994, Most et al. 2005, Salar, Faghih, and Pishdad 2016), and performed subgroup analyses based on the oil types. Thirdly, the participants recruited for the studies had similar primary cholesterol levels, since differences in the baseline TC value might have had a significant impact on the study results. Fourthly, the participants recruited for the trials did not use cholesterol-lowering medications, except for one study in which this issue was not mentioned (Lai et al. 2011). Fifthly, a highly accurate search and also a precise determination of the inclusion and exclusion criteria for entering the most similar studies into the analysis is another strength of the study. However, there are some limitations to this meta-analysis as well. Firstly, it was not registered in PROSPERO yet, due to the length of time it took to get the registration code. Secondly, we analyzed both cross-over and parallel studies which were different in terms of methods and biases and, due to the small number of parallel studies (Lai et al. 2011, Salar, Faghih, and Pishdad 2016), we were unable to perform subgroup analyses in this field. Thirdly, the oil doses were expressed only in a number of studies and therefore it was not possible to perform subgroup analyses to determine the effect of the dose of the testing oils on the lipid profile. Finally, the studies we evaluated had small sample sizes. Consequently, this suggests that further randomized clinical studies with larger sample sizes are needed to reduce any possible biases.

Conclusion

The results of our meta-analysis show that RBO can significantly decrease serum TC, LDL-c and TG levels in adults. In addition, the results of the subgroup analysis for BMI showed that the reduction of TC was significantly higher in participants with overweight *versus* normal weight and in subjects $\geq$50 years old, and also in comparison with oils rich in MUFAs. However, in the case of LDL-c the reduction was higher in subjects $<$50 years old. Also, the reduction of TC, LDL-c and TG was significantly higher when the duration of the intervention was $\geq$5 weeks. Therefore, RBO consumption might be efficient in improving the lipid profile of adult subjects and thus prevent the development of dyslipidemia/hyperlipidemia. However, for reliability and a higher replicability of the results, future clinical trials, with larger sample sizes, and different RBO doses are required in order to elucidate the effect of RBO consumption on serum lipids.

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Conflict of interest

All authors have no conflicts of interest to declare.

References

Abdelhamid, A. S., N. Martin, C. Bridges, J. S. Brainard, X. Wang, T. J. Brown, S. Hanson, O. F. Jimoh, S. M. Ajabnoor, K. H. Deane, et al. 2018. Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease. *The Cochrane Database of Systematic Reviews* 7 (7):CD012345CD012345. doi: 10.1002/14651858.CD012345.pub2.

Aida, A.,. T. Svensson, A. K. Svensson, U.-I. Chung, and T. Yamauchi. 2020. eHealth Delivery of Educational Content Using Selected Visual Methods to Improve Health Literacy on Lifestyle-Related Diseases: Literature Review. *JMIR mHealth and uHealth* 8 (12): e18316 doi: 10.2196/18316.

Armstrong, M. J., and M. C. Carey. 1987. Thermodynamic and molecular determinants of sterol solubilities in bile salt micelles. *Journal of Lipid Research* 28 (10):1144–55. doi: 10.1016/S0022-2275(20)38604-1.

Berger, A., D. Rein, A. Schäfer, I. Monnard, G. Gremaud, P. Lambelet, and C. Bertoli. 2005a. Similar cholesterol-lowering properties of rice bran oil, with varied gamma-oryzanol, in mildly hypercholesterolemic men. *Eur J Nutr* 44 (3):163–73. doi: 10.1007/s00394-004-0508-9.

Berger, A., D. Rein, A. SchäFer, I. Monnard, G. Gremaud, P. Lambelet, and C. Bertoli. 2005b. Similar cholesterol–lowering properties of rice bran oil, with varied γ–oryzanol, in mildly hypercholesterolemic men. *European Journal of Nutrition* 44 (3):163–73. doi: 10.1007/s00394-004-0508-9.

Bumrungpert, A., R. Chongsuwat, C. Phosat, and A. Butacnum. 2019. Rice bran oil containing gamma-oryzanol improves lipid profiles and antioxidant status in hyperlipidemic subjects: A randomized double-blind controlled trial. *The Journal of Alternative and Complementary Medicine* 25 (3):353–8. doi: 10.1089/acm.2018.0212.

Calvo-Castro, L. A., N. Sus, C. Schiborr, A. Bosy-Westphal, M. L. Duran, D. Fesenmeyer, G. Fesenmeyer, and J. Frank. 2019. Pharmacokinetics of vitamin E, γ-oryzanol, and ferulic acid in healthy humans after the ingestion of a rice bran-enriched porridge

prepared with water or with milk. *European Journal of Nutrition* 58 (5):2099–110. doi: 10.1007/s00394-018-1770-6.

Chen, C. W., and H. H. Cheng. 2006. A rice bran oil diet increases LDL-receptor and HMG-CoA reductase mRNA expressions and insulin sensitivity in rats with streptozotocin/nicotinamide-induced type 2 diabetes. *The Journal of Nutrition* 136 (6):1472–6. doi: 10.1093/jn/136.6.1472.

Chen, P. R., and C. E. Tsai. 1995. Various high monounsaturated edible oils might affect plasma lipids differently in man. *Nutrition Research* 15 (5):615–21. doi: 10.1016/0271-5317(95)00029-I.

Eady, S., A. Wallace, J. Willis, R. Scott, and C. Frampton. 2011. Consumption of a plant sterol-based spread derived from rice bran oil is effective at reducing plasma lipid levels in mildly hypercholesterolaemic individuals. *The British Journal of Nutrition* 105 (12): 1808–18. doi: 10.1017/S0007114510005519.

Fatahi, S., N. Namazi, B. Larijani, and L. Azadbakht. 2018. The association of dietary and urinary sodium with bone mineral density and risk of osteoporosis: A systematic review and meta-analysis. *Journal of the American College of Nutrition* 37 (6):522–32. doi: 10.1080/07315724.2018.1431161.

Friedman, M. 2013. Rice brans, rice bran oils, and rice hulls: Composition, food and industrial uses, and bioactivities in humans, animals, and cells. *Journal of Agricultural and Food Chemistry* 61 (45):10626–41. doi: 10.1021/jf403635v.

Fujiwara, Y. 2019. Preventive Effect of Polyunsaturated Fatty Acid and Vitamin E in Rice Bran Oil on Lifestyle-Related Diseases. *Journal of Nutritional Science and Vitaminology* 65 (Supplement):S34–S37. (Supplement):doi: 10.3177/jnsv.65.S34.

Ghobadi, S., Z. Hassanzadeh-Rostami, F. Mohammadian, A. Nikfetrat, n Ghasemifard, H. Raeisi Dehkordi, and S. Faghih. 2019. Comparison of blood lipid-lowering effects of olive oil and other plant oils: A systematic review and meta-analysis of 27 randomized placebo-controlled clinical trials . *Critical Reviews in Food Science and Nutrition* 59 (13):2110–24. doi: 10.1080/10408398.2018.1438349.

Ghobadi, S., Z. Hassanzadeh-Rostami, F. Mohammadian, M. Zare, and S. Faghih. 2019. Effects of Canola Oil Consumption on Lipid Profile: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. *Journal of the American College of Nutrition* 38 (2):185–96. doi: 10.1080/07315724.2018.1475270.

Harris, W. S., T. D. Dayspring, and T. J. Moran. 2013. Omega-3 fatty acids and cardiovascular disease: New developments and applications. *Postgraduate Medicine* 125 (6):100–13. doi: 10.3810/pgm.2013.11.2717.

Higgins, J. P. 2008. "Cochrane handbook for systematic reviews of interventions version 5.0. 1. The Cochrane Collaboration." http://www.cochrane-handbook.org.

Hooper, L., N. Martin, A. Abdelhamid, and G. Davey Smith. 2015. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev* (6):Cd011737. doi: 10.1002/14651858.cd011737.

Hozo, S. P., B. Djulbegovic, and I. Hozo. 2005. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 5 (1):13. doi: 10.1186/1471-2288-5-13.

Ishihara, M. 1984. Effect of gamma-oryzanol on serum lipid peroxide level and clinical symptoms of patients with climacteric disturbances . *Asia-Oceania Journal of Obstetrics and Gynaecology* 10 (3):317–23. doi: 10.1111/j.1447-0756.1984.tb00693.x.

Ito, Y., Y. Nakashima, and S. Matsuoka. 2015. Rice bran extract containing acylated steryl glucoside fraction decreases elevated blood LDL cholesterol level in obese Japanese men. *The Journal of Medical Investigation : JMI* 62 (1-2):80–4. doi: 10.2152/jmi.62.80.

Jolfaie, N. R., M. H. Rouhani, P. J. Surkan, F. Siassi, and L. Azadbakht. 2016. Rice bran oil decreases total and LDL cholesterol in humans: A systematic review and meta-analysis of randomized controlled clinical trials. *Hormone and Metabolic Research* 48 (07):417–26.

Kerckhoffs, D. A. J. M., R. P. Mensink, T. W. A. de Bruin, E. A. Trautwein, F. Brouns, and G. Hornstra. 2000. Tocotrienols from rice bran oil have no effects on levels of LDL cholesterol and markers for cholesterol synthesis and absorption. *Atherosclerosis* 151 (1):114. doi: 10.1016/S0021-9150(00)80517-1.

Kuriyan, R., N. Gopinath, M. Vaz, and A. V. Kurpad. 2005. Use of rice bran oil in patients with hyperlipidaemia. *National Medical Journal of India* 18 (6):292.

Kustiyah, L., M. Dewi, E. Damayanthi, C. M. Dwiriani, and D. Alamsah. 2019. Lipid Profile Improvement of Overweight-Obese Adults after High Antioxidant Tomato and Rice Bran Drinks Intervention. *Indian Journal of Public Health Research & Development* 10 (6):551–5. doi: 10.5958/0976-5506.2019.01332.9.

Lai, M.-H., Y.-T. Chen, Y.-Y. Chen, J.-H. Chang, and H.-H. Cheng. 2011. Effects of rice bran oil on the blood lipids profiles and insulin resistance in type 2 diabetes patients. *Journal of Clinical Biochemistry and Nutrition* 51:15−18.

Lichtenstein, A. H., L. M. Ausman, W. Carrasco, L. J. Gualtieri, J. L. Jenner, J. M. Ordovas, R. J. Nicolosi, B. R. Goldin, and E. J. Schaefer. 1994. Rice bran oil consumption and plasma lipid levels in moderately hypercholesterolemic humans. *Arteriosclerosis and Thrombosis: A Journal of Vascular Biology* 14 (4):549–56. doi: 10.1161/01.ATV.14.4.549.

Maurya, N. K., P. Arya, and N. S. Sengar. 2020. Hypolipidemic effect of rice bran oil on chronic renal failure (undergoing hemodialysis) patients.

Minhajuddin, M.,. Z. H. Beg, and J. Iqbal. 2005. Hypolipidemic and antioxidant properties of tocotrienol rich fraction isolated from rice bran oil in experimentally induced hyperlipidemic rats. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 43 (5):747–53. doi: 10.1016/j.fct.2005.01.015.

Moher, D., L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, and L. A. Stewart, PRISMA-P Group 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 4 (1):1 doi: 10.1186/2046-4053-4-1.

Moreau, R. A., B. D. Whitaker, and K. B. Hicks. 2002. Phytosterols, phytostanols, and their conjugates in foods: Structural diversity, quantitative analysis, and health-promoting uses. *Progress in Lipid Research* 41 (6):457–500. doi: 10.1016/S0163-7827(02)00006-1.

Most, M. M., R. Tulley, S. Morales, and M. Lefevre. 2005. Rice bran oil, not fiber, lowers cholesterol in humans. *The American Journal of Clinical Nutrition* 81 (1):64–8. doi: 10.1093/ajcn/81.1.64.

Murata, K., T. Kamei, Y. Toriumi, Y. Kobayashi, K. Iwata, I. Fukumoto, and M. Yoshioka. 2007. Effect of processed rice with brown rice extracts on serum cholesterol level. *Clinical and Experimental Pharmacology and Physiology* 34 (s1):S87–S89. nodoi: 10.1111/j.1440-1681.2007.04790.x.

Nhung, B. T., Tuyen, L. D. V. A. Linh, D. Van, N. T. T. Nga, V. T. M. Thuc, K. Yui, Y. Ito, Y. NAkASHIMA, and S. Yamamoto. 2016. Rice bran extract reduces the risk of atherosclerosis in post-menopausal Vietnamese women. *Journal of Nutritional Science and Vitaminology* 62 (5):295–302. doi: 10.3177/jnsv.62.295.

Oshima, S., S. Suzuki, and C. Imai. 1972. Effect of trial-mayonnaise on human serum cholesterol. *The Japanese Journal of Nutrition and Dietetics* 30 (5):203–5. doi: 10.5264/eiyogakuzashi.30.203.

Ostlund, R. E. Jr. 2007. Phytosterols, cholesterol absorption and healthy diets. *Lipids* 42 (1):41–5. doi: 10.1007/s11745-006-3001-9.

Purushothama, S., P. L. Raina, and K. Hariharan. 1995. Effect of long term feeding of rice bran oil upon lipids and lipoproteins in rats. *Molecular and Cellular Biochemistry* 146 (1):63–9. doi: 10.1007/BF00926883.

Qureshi, A., B. Bradlow, W. Salser, and L. Brace. 1997. Novel tocotrienols of rice bran modulate cardiovascular disease risk parameters of hypercholesterolemic humans. *The Journal of Nutritional Biochemistry* 8 (5):290–8. doi: 10.1016/S0955-2863(97)89667-2.

Raghuram, T. C., U. Brahmaji Rao, and C. Rukmini. 1989. Studies on hypolipidemic effects of dietary rice bran oil in human subjects. Nutrition Reports International (USA) *39 (5):889–95.*

Rajnarayana, K., M. C. Prabhakar, and D. R. Krishna. 2001. Influence of rice bran oil on serum lipid peroxides and lipids in human subjects. *Indian Journal of Physiology and Pharmacology* 45 (4):442.

Rukmini, C., and T. C. Raghuram. 1991. Nutritional and biochemical aspects of the hypolipidemic action of rice bran oil: A review. *Journal of the American College of Nutrition* 10 (6):593–601. doi: 10.1080/07315724.1991.10718181.

Salar, A., S. Faghih, and G. R. Pishdad. 2016. Rice bran oil and canola oil improve blood lipids compared to sunflower oil in women with type 2 diabetes: A randomized, single-blind, controlled trial. *Journal of Clinical Lipidology* 10 (2):299–305. doi: 10.1016/j.jacl.2015.11.016.

Sanders, T. A., and S. Reddy. 1992. The influence of rice bran on plasma lipids and lipoproteins in human volunteers. *European Journal of Clinical Nutrition* 46 (3):167.

Schwab, U. S., S. Vogel, C. J. Lammi-Keefe, J. M. Ordovas, E. J. Schaefer, Z. Li, L. M. Ausman, L. Gualtieri, B. R. Goldin, H. C. Furr, et al. 1998. Varying dietary fat type of reduced-fat diets has little effect on the susceptibility of LDL to oxidative modification in moderately hypercholesterolemic subjects. *The Journal of Nutrition* 128 (10):1703–9. doi: 10.1093/jn/128.10.1703.

Shakib, M.-C., S. Gabrial, and G. Gabrial. 2014. Rice bran oil compared to atorvastatin for treatment of dyslipidemia in patients with type 2 diabetes. *Open Access Macedonian Journal of Medical Sciences* 2 (1): 95–102. doi: 10.3889/oamjms.2014.017.

Suzuki, S., and S. Oshima. 1970. Influence of blending oils on human serum cholesterol (part 2). *The Japanese Journal of Nutrition and Dietetics* 28 (5):194–8. doi: 10.5264/eiyogakuzashi.28.194.

Tan, S.-Y., E. Peh, P. C. Siow, A. G. Marangoni, and C. J. Henry. 2017. Effects of the physical-form and the degree-of-saturation of oil on postprandial plasma triglycerides, glycemia and appetite of healthy Chinese adults. *Food & Function* 8 (12):4433–40. doi: 10.1039/C7FO01194F.

Tong, C., and B. Jinsong. 2019. Rice lipids and rice bran oil. " In *Rice*, 131–68. Eagan, Minnesota: Elsevier.

Trautwein, E. A., and S. McKay. 2020. The role of specific components of a plant-based diet in management of dyslipidemia and the impact on cardiovascular risk. *Nutrients* 12 (9):2671. doi: 10.3390/nu12092671.

Utarwuthipong, T., S. Komindr, V. Pakpeankitvatana, S. Songchitsomboon, and N. Thongmuang. 2009. Small dense low-density lipoprotein concentration and oxidative susceptibility changes after consumption of soybean oil, rice bran oil, palm oil and mixed rice bran/palm oil in hypercholesterolaemic women. *Journal of International Medical Research* 37 (1):96–104. doi: 10.1177/147323000903700111.

Vissers, M. N., P. L. Zock, G. W. Meijer, and M. B. Katan. 2000. Effect of plant sterols from rice bran oil and triterpene alcohols from shea-nut oil on serum lipoprotein concentrations in humans. *The American Journal of Clinical Nutrition* 72 (6):1510–5. doi: 10.1093/ajcn/72.6.1510.

Wang, O., J. Liu, Q. Cheng, X. Guo, Y. Wang, L. Zhao, F. Zhou, and B. Ji. 2015. Effects of Ferulic Acid and γ-Oryzanol on High-Fat and High-Fructose Diet-Induced Metabolic Syndrome in Rats. *Plos One* 10 (2):e0118135 doi: 10.1371/journal.pone.0118135.

Weststrate, J. A., and G. W. Meijer. 1998. Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects . *Eur J Clin Nutr* 52 (5):334–43. doi: 10.1038/sj.ejcn.1600559.

Wijayanthie, N., D. R. Gunarti, and N. R. Manikam. 2019. Effects of extra virgin olive oil versus rice bran oil on glycemic control in patients with type-2 diabetes mellitus. *International Journal of Applied Pharmaceutics* 11 (Special Issue 6):56–9. doi: 10.22159/ijap.2019.v11s6.33540.

Zavoshy, R., N. Mostafa, and J. Hassan. 2012. Effect of low calorie diet with rice bran oil on cardiovascular risk factors in hyperlipidemic patients. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences* 17 (7):626.e the 5th letter of the Roman alphabet More (Definitions, Synonyms, Translation)