ROS

REVIEW ARTICLE

An Insight into the Prophylactic Effects of the Leguminosae Family Plants against Oxidative Stress-Induced Pathophysiological Conditions

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ABSTRACT | Legumes are the protein-rich plants belonging to the large family Fabaceae (or Leguminosae). Fabaceae ranks third, in the family of higher plants, with around 20,000 members and just after cereal crops, they rank second in agricultural importance. Recently, the dietary supplements isolated from the legume plants have gained much popularity due to their lower toxicities and numerous health benefits. Different studies suggest that this plant family has several beneficial activities such as antioxidant, antibacterial, and estrogenic effects. Along with these, legumes are also known to possess several other medicinal properties in various organs and act as anti-diabetic, anti-cancer, anti-inflammatory, anti-osteoporotic, anti-nociceptive, anti-atherogenic, anti-nephritic, diuretic, digestive, laxative, sedative, chemo preventive, and as well as neuroprotective agents. Such therapeutic properties of legumes are due to the presence of different flavonoids, saponins, rotenoids, chalcones, glucosides, trypsin inhibitors, and alkaloids within them. Epidemiological data also suggests that legumes are effective in the treatment of several diseases such as diarrhea, kwashiorkor, bronchitis, rheumatic pain, and insomnia. This article encompasses important information about the current status and progresses made in legume-related research in the domain of natural products. It aims to overview different Leguminosae plants, their bioactive constituents, therapeutic effectivity, and hazardous health effects if any.

KEYWORDS | Anti-cancer activity; Anti-diabetic activity; Antioxidants; Legumes; Neuroprotective activity; Organ pathophysiology; Oxidative stress

ABBREVIATIONS | AGEs, advanced glycation end products; CNS, central nervous system; CTC, condensed tannin content; DGC, dehydroglyasperin; DPPH, 2,2-diphenyl-1-picryhydrazyl; FRAP, ferric-reducing antioxidant power; GLP-1R, glucagon-like peptide-1 receptor; GSH, reduced glutathione; GSSG, oxidized glutathione; HCC, hepatocellular carcinoma; IκB, inhibitory κ-B kinase; MAC, monomeric anthocyanin content; MAPK, mitogen-activated protein kinase; MM, multiple myeloma; ORAC, oxygen radical absorbing capacity; PNS, the peripheral nervous system; PPARγ, peroxisome proliferator-activated receptor-gamma; RNS, reactive nitrogen species (RNS); ROS, reactive oxygen species (ROS); SOD, superoxide dismutase; TFC, total flavonoid content; TPA, total phenolic content; Trx, thioredoxin

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1. INTRODUCTION

The important issue that has long been debatable is the basic difference between food and medicine. In the scenario of human evolution, the importance of plants has been gradually highlighted with time but their use pre-dates human history. Nearly 60,000 years ago during the Paleolithic age, humans started using plants with medicinal value (as suggested by a large number of archaeological evidence) [1]. Plants and their products served as food and shelter to mankind for millennia, but upon identifying their varied medicinal properties, the importance of plants increased hugely to mankind. Such plants with therapeutic properties are collectively termed as medicinal plants. Even some non-primates are known to consume medicinal plants during their illness. Thus, due to such beneficial effects of plants, the emergence of new concepts such as nutraceuticals, phytonutrients, nutritional therapy, and phytotherapy have appeared [2–6].

Till date, an extensive variety of medicinal plants are present, and they are found to produce an innumerable number of chemical compounds (12,000 isolated so far). These chemical compounds have a wide array of biological functions and act on the human beings through processes indistinguishable from conventional pharmaceutical drugs. Moreover, apart from their beneficial pharmacology, minimum or no side effects compared to conventional drugs make these herbal medicines a better option for treating ailments. Another advantage of using phytochemicals is their monetary affordability compared to modern pharmaceuticals. Thus, a good way to discover future medication is to research traditional plant uses on humans, a study popularly known as "ethnobotany".

Most of the contemporary pharmaceuticals derived from plants had a long term traditional use as herbal medicine with the same healing property. In some Asian and African countries, presently, 80% of the population use therapeutic phytochemicals for some aspect of medication and health care [7, 8]. The discovery of bioactive phytochemicals produced from plants having traditional medicinal value, due to their metabolic activity, provides high availability and is an expanding and progressing field. It is grossly estimated that around 67% of the existing drugs have a natural origin [9]. Moreover, most of the anticancer drugs used are also obtained from nature [10–12].

Such a large family of flowering plants having great medicinal and economic value is Fabaceae, more commonly known as Leguminosae or Papilionaceae [13]. They are normally identified as the legume, pea, or bean family. Different lines of molecular and morphological evidence (based on degree of interrelation revealed by different groups of this family) as well as DNA sequence based recent phylogenetic studies support the fact that the Fabaceae is a single monophyletic phytofamily [14–17]. Herbaceous plants (perennial or annual), shrubs, and even trees fall under the Leguminosae family and they are commonly characterized by their fruit or legume, leaves, and bioactive compounds.

The Latin word "faba" means "bean". As the name "Fabaceae" suggests, the fruits of these plants are bean shaped. Leguminosae is the valid but older name of this family only and it also refers to the fruits of this foliage, which are also termed legumes. The taxonomical classification of Fabaceae reports that it is categorized under the kingdom Plantae, division of Magnoliophyta, having the class and order of Magnoliopsida and Fabales, respectively. The most popular family of plants found in dry forests and tropical rainforests of America and Africa are the Fabaceae family [18]. According to the total number of species worldwide, Fabaceae ranks third in the list of terrestrial plant family with approximately 19,500 identified species and more than 600 genera [19–21]. The five major legume genera, classified according to the total number of identified species categorised under them (starting from around 2000 to 500 species), are Astragalus, Acacia, Indigofera, Crotalaria, and lastly Mimosa. These five genera together constitute nearly a quarter of the total legume species.

Regarding food source to animals and humans, the most important Graminae family is followed immediately by the Leguminosae family. Legumes being the rich sources of critical proteins are highly important crop plants forming a vital part of vegetarian diet around the world especially in developing countries. They also serve as animal feeds and important forage crops in horticulture.

2. LEGUMES AND THEIR IMPORTANCE TO MANKIND

In agricultural perspectives, legumes hold a very vital and unique niche as apart from serving as a food source, they possess extra nutritional qualities due to nitrogen fixation. In the present scenario of hiked prices of nitrogen fertilizers and huge exhaustion of energy sources, leguminous plants have fetched attention. These plants, by restoring soil fertility as well as atmospheric nitrogen, play an economically important role (due to their use in crop rotation and intercropping) in substantial development in agriculture. The huge diversity in heights, foliage, and flower of leguminous plants led to their use as ornamental plants for centuries. These varied uses make these plants both economically and culturally important [22–28].

Among the several classes of commercially farmed legumes, the important ones possess several beneficial roles. Among them, the main classes are grain, forage, blooms, pharmaceuticals, green manure, and timber species. The forage legumes are either grazed by livestock or sown in the pasture or they are broken down by livestock and humans for stock feed. Grain legumes, including both plants and trees, also called pulses, are cultivated for their seeds, used for consumption or industrial processes (to produce oils). Bloom legume species are commercially farmed for gardening worldwide. The plant, Indigofera, is cultivated for the industrial production of indigo. Hematoxylin, the widely used histological stain, is produced by the Leguminosae plant *Haematoxylon campechianum*.

Pharmaceutically significant legume includes Acacia and Derris, for gums and rotenone production respectively. Acacia species are also well known for their worldwide contribution to timber production. Apart from these, leguminous plants also contain fibers, vitamins, and minerals. Several parts of the plants along with their metabolites have great therapeutic importance as they are effective in treating different ailments traditionally as well as the enhancement of health and immunity in individuals consuming them as a regular part of diet. Their efficiency as a hormone producer is also well known. Thus, they are better known as dietary supplements rather than drugs.

From a commercial perspective, some of the most important Fabaceae species are soybean (*Glycine max*), pea (*Pisum sativum*), and peanut (*Arachis hypogaea*). According to the nutritionists, leguminous plants contain fibers, organic constituents, minerals, and vitamins like A, C, and E. The primary organic and mineral constituents include proteins, carbohydrates, fats, oxalate, phytic acid, calcium, magnesium, iron, zinc, potassium, and nitrogen. Further research showed their phytochemical constituents to be isoflavones, prenylated flavonoids, flavanones, flavanols, alkaloids, saponins, glucosides, tannins, rotenoids, chalcones, alkaloids, and trypsin inhibitors, with flavonoids being the largest and the important constituents of this Leguminosae family. The legume specific free amino acid, canavanine, is another constituent of legumes.

Different parts of the legume plants have medicinal value and exhibit healing properties against various ailments. Further extensive research on these plants (both in vivo and in vitro) reports them to possess therapeutic properties like antioxidant, anti-inflammatory, anticancer, antidiabetic, antinociceptive, antibacterial, antifungal, antiosteoporotic, insecticidal, laxative, digestive, sedative, antinephritic, diuretic, and neuroprotective effects, among others [29–33]. Legumes are also well known to show the protective effect by preventing diseased conditions like nervousness, insomnia, and stress and inhibiting ailments like ulcers, diarrhea, bronchitis, and rheumatic pain. Even regulation of energy metabolism and treatment of metabolic syndromes like kwashiorkor, hyperglycemia, and hypercholesterolemic conditions are carried out by legumes. Reports suggest that the antioxidant property of these plants is the main etiology behind the pluripotent activity of these plants. **Figure 1** illustrates the various bioactive properties exerted by the legume plant extracts/products. The chemical constituents in legumes that contribute to the antioxidant property along with the mechanistic approach towards their protective activity against different pathophysiological conditions are briefly described in this article.

3. NUTRITIONAL ELEMENTS OF LEGUMES

Legumes, precisely the grain legumes including peas, beans, lentils, and peanuts play an imperative role in the traditional human diets. Although consumed by all masses of people, the vegans, vegetarians, or people having plant-based food, more strictly have legumes as a part of their diet. Beans serve the primary part of a diet mainly because they are renowned for their rich protein content and even soluble-fiber content with exception to only soybeans which are rich in isoflavones. Legumes meet 15% of the RDA (recommended dietary allowance) for protein for an adult weighting 70 kg, as the protein content in them is quite high serving between 20% and 30% of energy. Due to the presence of less sulfur-containing amino acids in them, the protein-efficiency ratios of beans are quite low, and so the qualities of bean proteins are underestimated. However, on evaluating protein quality by PDCAAS (protein digestibility corrected amino acid score), the protein values were higher with some having the highest value available [34, 35]. Moreover, consumption of bean proteins is found to be associated with increased calcium retention in the body relative to animal proteins. Thus, regarding bone health, substituting bean protein (due to its hypocalciuric effect) for animal protein seems to be beneficial for the human body especially in individuals with hypercholesterolemia.

The fat content in the beans is very less with linoleic acid being the predominant fatty acid in beans, particularly soybeans. Fat in legumes serves only 5% of energy with marked exception to soybeans and chick peas having the fat energy of 47% and 15%. Docosahexaenoic acid and eicosapentaenoic acid are polyunsaturated fatty acids (PUFAs) present in beans widely studied for their health benefits [36–39]. **Table 1** lists the important bioactive components isolated from different Leguminosae family plants. The essential nutrient folate is present in huge amounts in beans where one serving of beans supports more than 50% of the recommended dietary allowance for folate.

The other important micronutrients present in different beans are riboflavin, iron, zinc, and calcium though regarding bioavailability, zinc and calcium surpass iron. Regarding dietary fiber, beans are an excellent source, increasing their popularity in the diet of hypercholesterolemic individuals. Also, due to the presence of tannin and phytic acid, beans have a significantly low glycemic index [40–43]. Thus, beans are particularly vital food for individuals having diabetes or with an eminent risk of developing diabetes. Apart from these nutritive components, some nonnutritive constituents of beans include trypsin inhibitors, phytate (inositol hexaphosphate), saponins, and oligosaccharides. **Table 2** provides a list of protein rich sources of legumes with respective calorie content per 100 g.

Finally, many reports specify legumes to serve as an excellent dietary source of natural antioxidants, explaining their crucial role in disease prevention and health advancement. The high total phenolic content is directly linked with their significant antioxidant activity [44].

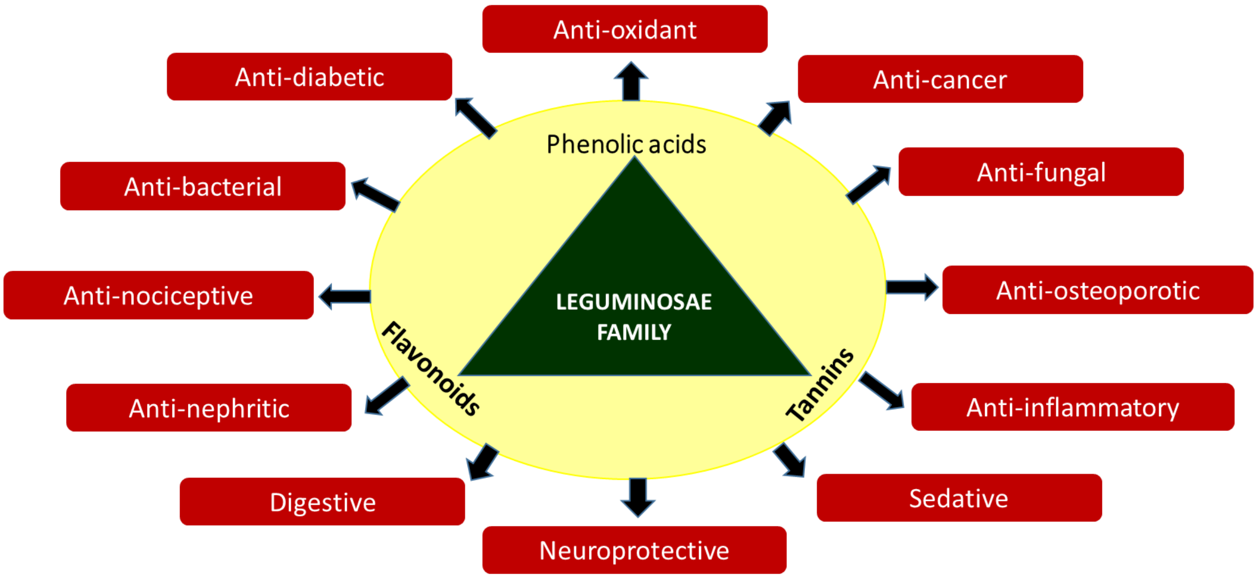

FIGURE 1. Various bioactive properties of legume plant products. See text for detailed description.

4. LEGUMES AS ANTIOXIDANTS

Various secondary metabolites from plant origin have shown great efficacy in treating numerous ailments. Most of these metabolites are bioactive molecules with anti-oxidative property [32, 33, 45]. In legumes, it is widely accepted that the class of dietary components exhibiting significant antioxidant activity is popularly known as phenolic compounds [46, 47]. Phenolic compounds can be broadly classified into three subgroups: phenolic acids, flavonoids, and tannins [48]. The secondary metabolites in plants derived from the important metabolic pathways like pentose phosphate, phenyl propanoid, and shikimate pathways are known as phenolic compounds [49]. Phenolic compounds usually consist of at least one aromatic ring with one or more than one hydroxyl group bonded to the aromatic moiety. Some factors, like the type of structure, number, and mutual positions of attached free hydroxyl groups, the site of mutual bonding [49, 50], and their ability to act as hydrogen or electron donating agents, determine the efficacy of these compounds acting as antioxidants.

Different experiments to estimate the percentage of phenolic content of different edible grains legumes like lentils, beans, the black bean, and the red kidney bean have been found to contain the maximum percent of total phenolic compounds [51]. The effects of thermal processing, i.e., boiling and steaming processes, at different pressures on the legumes especially their phenolic components, affect the individual phenolic acids. This processing significantly reduces the total phenolic acid content in comparison to the original beans (raw) and hampers the antioxidant properties of legumes. A study reports marked decrease in antioxidant profiles of processed pinto and black beans as evident from such parameters as total phenolic content (TPC), total flavonoid content (TFC), condensed tannin content (CTC), monomeric anthocyanin content (MAC), 2,2-diphenyl-1-picryhydrazyl (DPPH) free-radical scavenging activity, ferric-reducing antioxidant power (FRAP), and oxygen radical absorbing capacity (ORAC) values. The study once again confirms that phenolic components in legumes are the antioxidants accounting for legumes' antioxidant activity [52]. The properties and subgroups of the phenolic compounds are hereby discussed in detail.

4.1. Phenolic Acids

Phenolic acids are the derivatives of benzoic acids and cinnamic acids where in the basic aromatic ring, hydroxyl groups (-OH) and methoxy groups (-OCH_3)

TABLE 1. List of important antioxidant compounds in legumes

Class	Source	Bioactive compounds
Flavonoids	Black bean, red kidney bean, red peanut, soybean	Anthocyanidins, flavonols, flavones, flavan-3-ols, isoflavonoids, neoflavonoids
Phenolic acids	Bean, black bean, cowpea, lentil, navy lima bean, red kidney	Caffeic acid, ferulic acid, gallic acid, procatechuic, gallic acids, syringic acids, *p*-hydroxybenzoic, *p*-coumaric, sinapic acids, vanillic acid
Tannins	Common bean, chickpea, green pea, lentil, soybean, yellow pea	Condensed tannins, hydrolysable tannins

TABLE 2. Calorie chart of some important legume food products

Legume food product	Calorie per 100 g
Azuki beans	124
Black chickpeas	364
Green grams	347
Kidney beans	337
Lentils	353
Navy beans	337
Peanuts	567
Pecan	691
Pinto beans	347
Puy lentils	345
Red kidney beans	337
Roasted soybeans	471
Soy mayonnaise	322
Soy nut butter	562
Textured soy protein	571
Yellow lentils	304
White beans	336

at various points are substituted. These compounds exhibit antioxidant activity as they possess the abilities to decrease oxygen concentration, intercept singlet oxygen, bind metal ion catalysts, prevent 1st-chain initiation by scavenging initial radicals (e.g., hydroxyl radicals), decompose primary products (of oxidation) to nonradical species, and break chains from substances to prevent continued hydrogen abstraction [51, 53].

This phenolic group of antioxidant molecules can further be classified into hydroxybenzoic acids and hydroxycinnamic acids, having C6-C1 common structure. The major phenolic acids categorized under the class of hydroxybenzoic acids are gallic, *p*-hydroxybenzoic, procatechuic, vanillic, and syringic acids; whereas the main hydroxycinnamic acids are caffeic, ferulic, *p*-coumaric, and sinapic acids [22]. The main phenolic acids present in legumes are trans-ferulic acid [51], trans-*p*-coumaric acid, and syringic acid although reports also confirm the presence of *p*-hydroxybenzoic, protocatechuic, syringic, gallic, vanillic, caffeic, and sinapic acids in legumes [54, 55]. The highest amounts of phenolic acids are found in cowpea, navy bean, and lima bean whereas the lowest amounts of phenolic acids are reported to be found in pigeonpea, mungbean, field bean, lentil, and faba bean. Estimation of TPC in legumes has been carried out by different methods [51] with one common method being Folin-Ciocalteu assay. A report where TPC was measured by this method, suggested that black bean, black soybean, lentil, and red kidney bean have substantial total phenolic content compared to green pea, chick pea, yellow pea, and yellow soybean. Interestingly, the legumes having low TPC had smaller variations in results compared to legumes having higher TPC when different extraction solvents were used.

4.2. Flavonoids

Flavonoids are low molecular weight phenolic secondary metabolites ubiquitously found in plants (Kapoor). They help in root nodulation and self-defense of plants. The antioxidant defenses present in legume nodules are thought to help in the prevention of oxidative damage of crucial components of the nitrogen fixing system, such as the lipids of symbiosome membranes, the proteins nitrogenase, leghemoglobin, and glutamine synthetase, among others. Flavonoids as important components of several edible vegetables, legumes, and fruits (where they are present in either glycoside or aglycone form) are always consumed by humans. Flavonoids are diverse in structure with the antioxidant property common in all of them. This chemical property supports the epidemiological data that the consumption of food rich in flavonoids defends against oxidative stress-associated human ailments. Both in vivo and in vitro data suggest that flavonoids from plant sources exhibit free radical-scavenging activity and show protection against oxidative stress.

Chemically, flavonoids have the general structure of a 15-carbon skeleton with three pyran or aromatic rings. To be more specific, it consists of a benzopyran nucleus with three heterocycles in its backbone; two phenyl rings designated as A and B, and heterocyclic ring C, with an aromatic substituent at its C2. The ring A follows a phloroglucinol substitution pattern. Structurally, this carbon structure skeleton is abbreviated as C6-C3-C6. The IUPAC nomenclature of flavonoids classifies them into three groups, all of which are ketone containing compounds. Precisely the groups are flavones or flavonols (earlier termed as flavonoids or bioflavonoids), isoflavonoids derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone), and neoflavonoids derived from 4-phenylcoumarine (4-phenyl-1,2-benzopyrone).

Flavonoids are again classified into different classes by the position of the B ring and the substitution pattern of C ring. The main subgroups are flavonols, flavanones, isoflavones, anthocyanidins, and flavones. Flavonoids exhibit antioxidant activity by stabilising free radicals. The hydroxyl groups of the B-ring donate hydrogen and electrons to hydroxyl and peroxyl radical as well as peroxynitrite giving rise to relatively stable flavonoid radicals [56]. The flavonoids present in legumes are mainly flavonols, flavan-3-ols, flavones, and anthocyanidins [57–61]. There are different methods for the determination of total flavonoid content in legumes. Whereas the antioxidant efficacy of legumes can be determined by different assays like DPPH assay, free radical scavenging, FRAP assay, and ORAC assay. Soybean, red kidney bean, red peanut, and black bean are rich in flavonoids like genistein, daidzein, and glycitein are potent antioxidants. Among these, the isoflavonoid, genistein, is a widely studied molecule having multivariate properties because apart from being a potent antioxidant it has an additional feature of mimicking the important human reproductive hormone, estrogen. As such, genistein also called a phytoestrogen, is capable of binding to estrogen receptors and modulating a number of signaling cascades regulated by estrogen. Moreover, it can also effectively and selectively inhibit tyrosine kinase, and is thus thought to be a miraculous nutraceutical molecule with multivariant properties. In the human diet, the primary need of isoflavones is almost exclusively met by soybean (especially rich in genistein) in comparison to different legumes.

4.3. Tannins

Tannins are bioactive nutritionally beneficial compounds with high molecular weight and are rich in phenolic hydroxyl groups. They are broadly divided into two main types: the hydrolysable and condensed tannins (polymers of flavan-3-ols). When phenolic carboxylic acids are esterified to sugars, they lead to hydrolysable tannins. This class of tannins is so named because upon hydrolysis they lead to break down of sugars and phenolic acids. Condensed tannins, also known as proanthocyanindins, are formed through the condensation of flavanols. Earlier, it was thought that phenolic compounds are primarily found in the seeds of pigmented sorghum, millets, and legumes.

The predominant phenolic compounds in legume, especially its seeds, are the condensed tannins. They are widely present in pea, lentil, soybean, and common bean [62–65]. Tannins, located primarily in the testa, play a vital role in defense of seeds from oxidative damage due to environmental factors [63]. Condensed tannin content yields differ in different solvent extractions. In this context, methods for laboratory extraction of condensed tannins from different parts of forage legumes were developed as early as in 1976. Studies show that for extraction of condensed tannins from chickpea, green pea, yellow pea, soybean (both yellow and black), lentil, and red kidney bean, 80% acetone was the best compared to other concentrations of acetone. On the other hand, for the extraction of condensed tannins from black bean, the acidic 70% acetone was found to be the best.

5. OXIDATIVE STRESS, CELLULAR DYSFUNCTION, ORGAN PATHOPHYSIOLOGY AND ANTIOXIDANTS

5.1. General Considerations

In the last twenty years, a reasonably new thought about the role of oxidative stress (imbalance between the intracellular antioxidants and pro-oxidants in a living system) has been extensively implicated in biomedical sciences to define several pathophysiological states. The term "oxidative stress" was highlighted in the early 1950s, when the researchers started considering about the harmful effects of free radicals, ionizing radiation, and the comparable toxic effects observed by molecular oxygen, and the crucial role of those processes in the phenomenon of aging. Later on, the term began to be frequently used especially after 1970s [66]. Probably due to the theoretical, hypothetical, and the evanescent nature of free radicals and the lack of experimental tools to study them, the acceptance of these radicals was rather slow at the beginning of the active research of free radical biology. Oxidative stress, however, is a broader term than free radical biology, as few oxidants are free radicals. Thus, free radical biology and oxidative stress are neither synonymous nor interchangeable [67].

Reactive oxygen species (ROS) and free radicals are non-synonymous to each other since not every ROS is a free radical. A significant role is played by oxidative stress in the pathophysiology of many prevalent diseases such as hypertension, diabetes, preeclampsia, atherosclerosis, acute renal failure, Alzheimer's disease, and Parkinson's disease [68].

Physiological processes, such as mitochondrial respiration as well as pathophysiological conditions such as inflammation, foreign compound metabolism, radiation, and many other disorders expose cells to many oxidants [69]. Harmful ROS are generated during cellular metabolism of oxygen. The family of ROS consists of highly reactive species, which can be beneficial for some physiological functions; for example, the immune system uses them to attack and kill pathogens. ROS are continuously generated in organisms and are effectively eliminated by several intrinsic antioxidant defenses (e.g., proteins, enzymes, vitamins, and oligo elements) in normal physiological conditions [70–72]. However, a substantial impact of increased ROS levels on the cells leads to defective cellular functions, aging, and disease [73–78]. All the systems of our body are affected by oxidative stress. Every organ starting from the brain, kidney, skin, heart, spleen, liver, pancreas, and even the reproductive organs can be affected by it [70, 71, 79, 80].

Indirect evidence found by monitoring the levels of markers such as ROS, reactive nitrogen species (RNS), and antioxidant defense molecules, indicates that oxidative damage is responsible for the pathogenesis of different kinds of diseases [81, 82]. Oxidative stress is reported to play an important role in pathophysiological conditions such as organ dysfunctions, metabolic ailments, and cancers [83]. Probably, the age-related development and progression of cancer can be explained by the increasing levels of reactive species with age. The reactive species produced in oxidative stress are mutagenic and they can directly damage the DNA [84]. Further, they may also promote steps of cancer including cancer cell proliferation, invasiveness, and metastasis, by suppressing apoptosis [83]. By increasing the level of intracellular ROS and RNS in the human stomach, *Helicobacter pylori* cause gastritis and may lead to development of gastric cancer [85].

The expression of several genes involved in signal transduction is induced by ROS [73, 76, 86]. A higher ratio of reduced glutathione/oxidized glutathione (GSH/GSSG) is essential for protecting the cell from the damage due to oxidative stress. An imbalance in this ratio causes activation of many redox sensitive transcription factors, like NF-κB, AP-1, nuclear factor of activated T cells, and hypoxia-inducible factor 1, which are involved in inflammatory responses. Signal transduction cascades that transmit the information from outside to the inside of cell leads to activation of these transcription factors mediated by ROS. Many receptors and enzymes are the targets of ROS which include tyrosine kinase receptors, most of the growth factor receptors, like vascular endothelial growth factor receptor, epidermal growth factor receptor, and receptor for the platelet-derived growth factor, protein tyrosine phosphatases, and serine/threonine kinases, among others. The oxidants can also regulate different extracellular signal-regulated kinases, which belong to the mitogen-activated protein kinase family like JNK and p38, involved in several processes in normal cellular physiology including proliferation, differentiation, and apoptosis [87, 88].

The cysteine residues of the DNA-binding site of c-Jun, some AP-1 subunits, and inhibitory κ-B kinase (IκB) undergo reversible *S*-glutathionylation under oxidative stress conditions. Thioredoxin (Trx) and glutaredoxin have been reported to have a critical role in the regulation of oxidative stress-induced signaling pathways, such as AP-1, NF-κB, JNK, and p38 mitogen-activated protein kinase [88, 89]. Upon exposure to oxidative stress-related factors, such as ROS, free radicals, and UV irradiation, NF-κB is activated.NF-κB is free to translocate to the nucleus after phosphorylation of IκB and activates gene transcriptions. The serine residues of IκB have been reported to be phosphorylated by several kinases. Oxidative signals target those kinases to activate NF-κB. The DNA-binding activity of NF-κB is improved by reducing agents and inhibited by oxidizing agents [90]. Two opposite actions are exerted by Trx, in the regulation of NF-κB: it blocks degradation of IκB in the cytoplasm and inhibits its activation, and it enhances the NF-κB DNA binding in the nucleus. The activation of NF-κB by oxidation-related degradation of IκB in turn results in the activation of several antioxidant defense-related genes [91, 92].

The expression of several genes associated with oxidative stress such as IL-1β, IL-6, tumor necrosis factor-α, IL-8, and several other adhesion molecules that participate in immune response are regulated by the activity of NF-κB [93–95]. In addition, NF-κB regulates angiogenesis, proliferation, and differentiation of cells. The redox state of the cell is critical in the regulation and activity of AP-1. Some metal ions can induce activation of AP-1 in the presence of H_2O_2. A higher ratio of GSH/GSSG promotes AP-1 binding with DNA, while GSSG inhibits the binding. By the reduction of a single conserved cysteine in the DNA-binding domain of each of the proteins, there is enhanced binding of Fos/Jun heterodimer with the DNA. The DNA binding of AP-1 can be inhibited by GSSG in many cell types, indicating that disulfide bond formation by cysteine residues inhibits the binding of AP-1 to DNA [95, 96].

Our body has a number of antioxidants that help to counteract the oxidants and maintain their balance. These mechanisms can be divided into two categories: enzymatic and non-enzymatic. The first line of cellular defense against oxidative stress is the cellular antioxidant enzymes. The most extensively studied cellular antioxidants are the antioxidant enzymes, superoxide dismutase (SOD), catalase, glutathione reductase, and glutathione peroxidase. The most important antioxidants found in the body are SODs (specifically its isoforms, namely, Cu,ZnSOD and MnSOD) because their depletion causes tissue degeneration and overexpression delays cell death during oxidative insult in the tissue [75, 76, 97, 98]. Although not much is known, the peroxiredoxins are another important antioxidant enzymes effective against oxidative stress-mediated pathophysiological conditions. Another recently discovered and important enzymatic antioxidant is sulfiredoxin [98]. Glutathione-S transferases, paraoxonase, and aldehyde dehydrogenases are some other enzymes which play not only divergent primary roles but also possess antioxidant properties. The non-enzymatic molecules like GSH and melatonin also play critical roles as antioxidants [99–101].

GSH, a cysteine-containing peptide, is synthesized from constituent amino acids in the cells. GSH is found to be one of the most important cellular antioxidants in the brain as well as all the other major organs due to its high concentration and the central role in sustaining the cell's redox state. It possesses antioxidant properties due to the presence of a thiol group present in its cysteine moiety and thus can act as a reducing agent and can be reversibly oxidized and reduced. Normally, the enzyme glutathione reductase, maintains glutathione in its reduced form, GSH, and GSH in turn reduces other enzyme systems as well as metabolites. Under oxidative stress, GSH gets oxidized to form GSSG [102]. The ratio of GSH/GSSG is studied as a marker of oxidative stress. Melatonin is another powerful antioxidant and it can easily cross cell membranes and the blood-brain barrier. Melatonin does not undergo redox cycling (the ability of a molecule to undergo reduction and oxidation in a cyclic manner), like glutathione and other antioxidants [103]. Once it gets oxidized, it cannot go back to its reduced state and is therefore referred to as terminal or suicidal antioxidant (upon reacting with free radicals, many stable end products are formed).

Serious penalty in normal cellular mechanisms is caused due to imbalanced defense mechanism of cellular antioxidants, leading to oxidative damage to all the components of the cell including the macromolecules (protein, lipids, and nucleic acids). Also, this leads to peroxidation and carbonylation of lipids and proteins, respectively [104]. ROS cause strand breaks and base damages in the DNA. A number of pathophysiological conditions arise from the disruption of pro-oxidant/anti-oxidant balance or normal redox state of a cell due to interference in the primary cellular defense [105].

Antioxidant compounds protect the cell against the injury originated by unstable molecules, such as singlet oxygen molecule, superoxide molecule, peroxyl radicals, hydroxyl radicals, and peroxynitrite [83]. Antioxidant molecules decelerate or avoid the oxidation process of other micromolecules. As discussed earlier, oxidation reactions play an important role in everyday human life, and they can also be harmful. Therefore, diverse systems of various antioxidants are found in plants as well as animals such as glutathione, lycopene, beta-carotene, carotenoids, selenium, flavonoids, and natural vitamins together with vitamin C, vitamin A, vitamin E, and several antioxidant enzymes, including superoxide dismutase, glutathione *S*-transferases, glutathione peroxidase, and catalase, along with proteins that diminish the accessibility of free redox-active metal ions, such as ferritins, metallothioneins, and heme protein. As a result of discrepancy among antioxidant molecules and different reactive species, ROS and RNS mediate endothelial damage or cellular damage occurs in tissues or organs.

Oxidative stress originated from the excessive generation of reactive oxygen species has recently emerged as an important element of many human disorders/diseases. Thus, intensive studies on antioxidants are being carried out in the field of medicine, predominantly as management for inflammation and other related metabolic disorders like diabetes mellitus, cardiac diseases, cancer, and neurodegenerative diseases [106].

There are two categories of antioxidants: natural and synthetic antioxidants. Natural antioxidants are also known as the chain breaking antioxidants, which act in response to lipid free radicals and change them into highly stable end products. Mostly they are the following. (i) Vitamins: Vitamins (e.g., ascorbic acid, alpha-tocopherol, and vitamin B and its subtype) are the vital components and are essential for metabolic activities [107, 108]; (ii) Mineral antioxidants: The minerals act as cofactors of important enzymatic antioxidants and play dynamic roles in metabolism of several macromolecules, such as carbohydrates and nucleic acids. Mineral antioxidants include selenium, copper, iron, zinc, and manganese, among others [108]; (iii) Phytochemicals: These include flavonoids, catechins, carotenoids, β-carotenoids, and lycopene. The flavonoids account for the colors of the leaves, flowers, vegetables, fruits, grains, seeds, and bark due to the presence of the phenolic complex compounds [109]. Green and black tea, as well as sesamol contain catechins as the major bioactive antioxidants. Fruits and vegetables contain carotenoids, the fat-soluble pigment. Huge amounts of beta-carotenes are available in carrots and are transformed into vitamin A if nutritional deficiency of vitamin A is detected. Lycopenes, known for their cancer fighting ability, are the red pigments and reported to be an important phyto-constituent of certain vegetables and fruits including tomatoes [110].

Synthetic antioxidants include the phenolic group of compounds and perform the important function of scavenging free radicals, diminishing oxidative stress, and impeding the chain reactions through various biological actions. Some examples are butylated hydroxyl anisole (BHA), butylated hydroxyl toluene (BHT), tertiary butyl hydroquinone (TBHQ), esters of gallic acid (propyl gallate), ethylenediaminetetraacetic acid (EDTA), and nordihydroguaiaretic acid (NDGA) [111].

5.2. Sources and Origin of Antioxidants

Abundant antioxidants are present in leafy vegetables, fruits, and natural food sources especially lemon, amla, ashwagandha, and shatavari, in addition to nuts, grains, meats, chicken, and fish. Biologically active antioxidants such as beta-carotene are found in various colored fruits including orange, sweet potatoes, carrots, squash, apricots, pumpkin, and mangoes [112]. Few green leafy vegetables, including collard greens, spinach, and kale, are the abundant source of beta-carotene too. These vegetables are also rich in lutein which is best recognized as vital for healthy eyes [113, 114]. Selenium, a mineral component of antioxidant enzymes is found in rice and wheat, the chief dietary sources in many developing and developed countries. Recent studies reported that animals that grow in abundance of selenium in soil have high amount of selenium in their body muscle. The usual sources of dietary selenium in the United States are Brazil are nuts, meats, and bread [114]. Cinnamic acids, coumarin derivatives, diterpenes, flavonoids, monoterpenes, phenylpropanoids, tannins, and triterpenes are some phyto-constituents with antioxidant potential. All parts of higher plants like

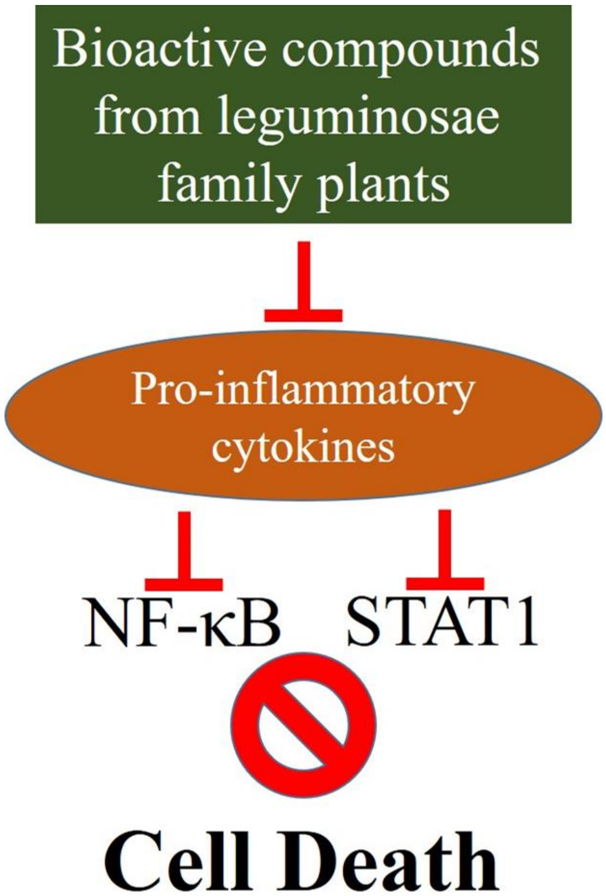

FIGURE 2. Inhibition of various signaling cascade induced by bioactive components of lugume plant attenuates cell death. See text for detailed description.

wood, bark, stems, pods, leaves, fruits, roots, flowers, pollens, and seeds are the sources of natural antioxidants. Lipoxygenases pathway is activated during injury to plant cells, and the occurrence of these signaling cascades in response to oxidative stress in plants clarifies why a plenty of antioxidant compounds have been recognized in plant tissues. Mostly those plants with elevated levels of powerful antioxidant compounds have an essential role in cure and treatment of illness concerning oxidative stress [75, 115].

Epidemiological studies suggest that the natural antioxidants, such as vitamin E, vitamin C, and β-carotene, may be beneficial in preventing several chronic disorders, and they can be obtained from dietary sources. These antioxidant molecules have drawn considerable interest in the possible reinforcement of antioxidant defenses. Apart from the epidemiological studies, several research reports from our lab and other labs around the globe suggested a prophylactic role of several naturally occurring antioxidants against different pathophysiological conditions associated with oxidative stress [116]. Some of the important active molecules in such studies include arjunolic acid, mangiferin, taurine, curcumin, resveratrol, silymarin, silybinin, genistein, and morin. An antioxidant must fulfil two fundamental conditions: (i) the compound must be present in low concentrations relative to the substrate to be oxidized and (ii) the species resulting from its oxidation must be stable through the formation of intramolecular hydrogen bonds [117].

Thus, a better understanding of the roles of ROS-mediated signaling in normal cellular function as well as in various diseases is needed for developing therapeutic tools for oxidative stress-related pathophysiological conditions. In this article, we discuss the beneficial efficacy of various antioxidants isolated from different Leguminosae family plants, in the light of a number of reported experimental studies. The use of antioxidants and preconditioning to protect an organism against ROS is also discussed in many research reports from our lab and others around the world.

6. THERAPEUTIC POTENTIAL OF LEGUMINOSAE FAMILY PLANTS IN OXIDATIVE STRESS-ASSOCIATED CONDITIONS

Various forms (e.g., concoctions or infusions and maceration) of different plant extracts are used in the traditional medicinal system to treat a wide range of pathophysiological conditions. Different parts of the legume plants are found to be useful for the cure of various ailments [118]. Many Leguminosae family species have shown beneficial effects on health. The research is accelerated for alternative medication based on plant extracts in western countries. The medicinal effect of Leguminosae is observed in different systems of the body. In this context, the possible use of soybean in functional food design is very interesting, since the consumption of soybean protein and dietary fibers seems to reduce the risk of cardiovascular diseases and to improve glycemic control [119]. Pharmacological studies have revealed the antibacterial, antifungal, antihypertensive, anti-oxidant, antiviral, anti-feedant, insecticidal, diuretic, and hypoglycemic properties, as well as hepatoprotective, nephroprotective, and cytotoxic effects (activities) of the plants of the leguminosae family [120–122]. Some Leguminosae species are used to treat polymenorrhagia, anemia, ulcers, and during pregnancy [123, 124]. Moreover, they also help in the treatment of diarrhea, in overcoming the protein deficiency disease, Kwashiorkor, and can also impact on the hypercholesterolemic conditions and thyroxine-induced hyperglycemia [125].

Different reports suggest that the products of Leguminosae family plant are used to treat bronchitis and can effectively cure illnesses in the upper breathing system, rheumatic pain, and gland inflammation. In **Figure 2**, the molecular targets, in response to inflammation, of the legume plant extracts/products are shown briefly. Leguminosae plant products have been shown to regulate insomnia, stress and nervousness, attenuate melanogenesis and normalize energy expenditure and metabolism [126, 127]. There are many other medicinal properties of Leguminosae family like anti-osteoporotic, anti-diabetic, anti-cancer, anti-nociceptive, anti-atherogenic, anti-inflammatory, anti-nephritic, laxative, sedative, diuretic, digestive, chemopreventive, and neuroprotective activities. Some of these important therapeutic properties of these Leguminosae plants are described comprehensively elsewhere [121], and summarized below.

6.1. Cancer

Despite various advances in medical therapeutics across the world, cancer continues to account for more than fourteen million new cases and around eight million deaths each year. Such an alarming increase in global incidence of cancer over the past several years has led to campaigns especially focused on disease prevention. Significant declines in global cancer incidence have been achieved through efforts such as tobacco cessation movements and vaccinations. Diet and exercise may have significant impact on the prevalence of specific types of cancers, renewing interest in dietary phytochemical research, as revealed by epidemiological studies [128, 129]. Some phytochemicals are mainly responsible for host protection against viruses, parasites, and other externally damaging agents. Preliminary studies have shown that these compounds can affect cell proliferation and cell cycle regulation [130]. They usually participate in multiple signaling pathways which are often disrupted in tumor initiation, proliferation, and propagation (**Figure 3**).

Although efforts till date have led to multiple successful pre-clinical studies, only a limited number of clinical trials have been carried out to completely explore the distinct impact of each dietary phytochemical on cancer prevention and progression. The failure of the several attempts in these clinical trials has been attributed to the variable bioavailability and distribution of these compounds, ideal dose of several natural products, and the significant reduction in the risk that may take many years to detect in large clinical studies [131]. As the incidence of cancer continues to rise globally, understanding the impact of these dietary phytochemicals may fuel simple and cost-effective ways to recover different pathophysiological conditions worldwide [132].

In recent studies, a phytoestrogen, bakuchiol, isolated from a Fabaceae family plant *Psoralea corylifolia L.* showed significant antiproliferative and anticancer effect against breast cancer [133]. It can effectively induce cell cycle arrest in S phase by blocking the activation of cyclin-dependent kinases (Cdc2) along with the upregulation of different pro-apoptotic signaling pathways. Another plant extract from the Fabaceae genus, *Erythrina excels* also exhibits growth inhibitory properties at lower doses on human breast and colon carcinoma cells [134]. Among the different compounds or plant extracts from the legume family, significant anticancer activity was shown by the different soy products. These soy products are a rich source of different isoflavones, namely, genistein, glycitein, and daidzain. Genistein can prevent the progression of angiogenesis by regulating different signaling molecules like MMPs, VEGF, and EGFR. It can also modulate the expression of NF-κB, PI3-K/Akt, m-TOR, and ERK1/2 to prevent the proliferation of the cancer cells [135]. Although at higher concentrations these soy isoflavones inhibit cellular proliferation in breast cancer cells, at lower doses they can stimulate the growth of ER positive breast cancer cells [136].

These soy derived phytochemicals can inhibit the activity of enzymes like 5α-reductase, protein histi-

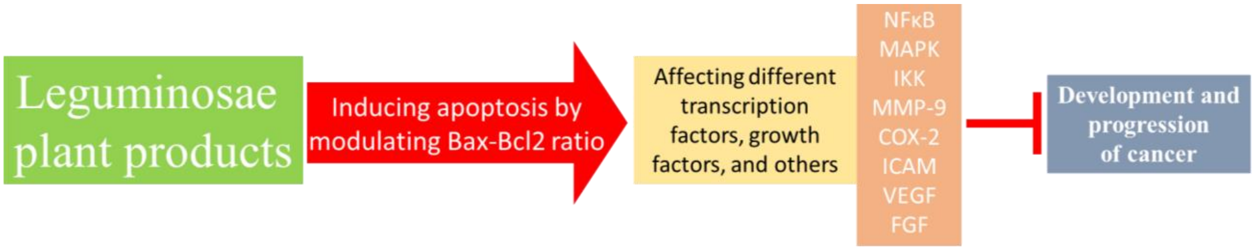

FIGURE 3. Legume plant products are capable of attenuating all the stages of cancer progression via the modulation of different signaling cascades. See text for detailed description.

dine kinase, and CDKs [137–140]. They can modulate different cell proliferative pathways by regulating the signaling molecules such as NF-κB, Akt, and MAPK and can also induce cell death [141]. In a recent study by Xie et al., the effectivity of genistein on multiple myelomas (MM) is reported. Genistein has also been found to regulate NF-κB and microRNA-29b (miR-29b) in the MM cells. It is also reported to induce apoptosis and inhibit angiogenesis in U266 cells [142]. Apart from these soy derived isoflavones, phytochemical compounds from another leguminosae plant Derris scandens, i.e., 5,7,4'-trihydroxy-6,8-diprenylisoflavone (TD) and lupalbigenin (LB), were proved to be dose dependently effective against various breast and colon cancer cells from humans and mice. These two compounds have the potential to arrest the cell cycle in the G2/M phase and can activate the intrinsic pathway of apoptosis [143]. In another study, it was found that LB significantly down-regulated several cell survival proteins like extracellular signal-regulated kinase (pERK/ERK) and protein kinase B (pAKT/AKT) to promote cell death and inhibit the metastasis of human lung cancer cells [144]. A Chinese herb from the Leguminosae family, *Astragalus membranaceus* Bunge plant extract has been found to be effective against hepatocellular carcinoma (HCC) by modulating the TGF-β/Smad and MAPK signaling pathway. It can also down-regulate the expression and nuclear transport of Imp 7 and can in turn block the expression of PAI-1 to inhibit the growth, proliferation, and metastasis of HCC cells at multiple target sites. *Glycyrrhiza inflate*, a legume family plant contains a water-soluble polysaccharide bioactive compound effective against human oral cancer cells, SCC25. It can activate the intrinsic apoptotic pathway and induce cell death in a caspase dependent manner [145]. Isoangustone A, a bioactive compound identified in the hexane/ethanol extract of *Glycyrrhiza uralensis* could also induce apoptosis in the human prostate cancer cell line, DU145 [146].

Overall, we found that different active compounds have been isolated from several Leguminosae family plants, and those compounds are active against many types of cancer cells. These compounds can potentially inhibit the development and progression of cancer.

6.2. Diabetes

An important risk factor for the onset of type 2 diabetes is insulin resistance. Although indirect, a common cause of insulin resistance is obesity [147]. Oxidative stress is broadly known to be critical in the development and progression of type 2 diabetes by disturbing the β-cell mass unswervingly or insulin sensitivity [148]. A study on rodents interestingly revealed lower levels of gene expression of the antioxidant enzymes, superoxide dismutase, catalase, and glutathione peroxidase, in β-cells than in other tissues. Again, a major factor in β-cell mass decrease is oxidative stress [149].

Extensive investigation on antioxidants is being carried out because of their ability to suppress oxidative stress and promote disease prevention and health maintenance [150]. Antioxidants primarily scavenge different free radicals in the cellular compartments and provide protection against reactive species mainly ROS and RNS. Traditionally, radical chemical initiators have been used for investigating radical-scavenging effects [118]. Different soy-derived isoflavones have a major role in the prevention of development of the pathophysiological states associated with diabetes [151]. The biological functions of antioxidants have been widely assessed from the perspective of their effects on the expression of antioxidant enzymes. For a complete evaluation of the in vivo physiological effects and biological fate of an antioxidant, it is crucial to define both properties (i.e., free radical-scavenging activity and effect on enzyme expression). For example, genistein is comparatively a mild radical-scavenger than the other polyphenolic antioxidants [71, 72]. However, the metabolic intermediates react readily with thiols to stimulate the transcription factor, nuclear factor (erythroid-derived 2)-like-2 (Nrf-2). This activation leads to the expression of several antioxidant enzymes, for example, heme oxygenase-1 (HO-1), gamma-glutamylcysteine ligase (γGCL), and NAD(P)H:quinone oxidoreductase 1 (NQO1). Several studies have shown that dietary lugume plant products like pegion peas, soya bean, and field bean have both anti-hyperglycemic and anticholesterolemic action.

Genistein inhibits insulin resistance and fat accumulation in different organs of the experimental animals having high calorie diet. It can inhibit the accumulation of fat in organs by the inhibition of p70 ribosomal S6K. It can also facilitate insulin signaling by modulating the activity of adenosine monophosphate-activated protein kinase (AMPK) [152, 153]. In type 2 diabetes mellitus, dietary supplementation of genistein and (*S*)-equol (a metabolite of diadzine) is found to be effective against the pathophysiological conditions. It can modulate the expression of an insulin-inducible transcription factor SHARP-2 and regulate the blood glucose level [154, 155]. Genistein can also modulate the activity of GLUT-1, a glucose transporter and inhibit the cellular uptake of glucose [156]. It is also capable of improving the survivability of the pancreatic β-cells by suppressing the expression and activity of iNOS and NO production induced by different cytokines. Along with these factors, genistein and its metabolites can modulate the JAK-STAT pathway responsible for the survival of the pancreatic cells [157, 158].

Bavachin, a compound isolated from a legume family plant, *Psoralea corylifolia L.* has been found to have an effective anti-hyperglycemic effect. It accumulates in the adipocytes and can activate different adipogenic transcription factors, including CCAAT/enhancer binding protein-α (C/EBPα) and peroxisome proliferator-activated receptor-gamma (PPARγ). It can alter the cellular glucose uptake by modulating the activity of GLUT-4 and the activity of pAKT as well as AMPK regardless of the presence of insulin [159]. Different bioactive isoflavones from chickpea are also reported to regulate the expression of GLUT-4, and along with this, those phytochemicals can also alter the expression of the acid-binding protein (ap2), uncoupling protein-2 (UCP-2), and lipoprotein lipase (LPL) in pre-adipocytic cells (3T3-L1 cells) [160]. In a recent work by King et al., it is reported that the extract of the fenugreek seed has the potential to regulate the signaling pathway mediated by glucagon-like peptide-1 receptor (GLP-1R) [161]. The GLP-1R is active in several tissues and has different physiological functions like energy homeostasis and cognition. GLP-1 analogs are accepted to treat patients with type 2 diabetes. These analogs are currently undergoing clinical trials for other diseases, including several cardiovascular disorders.

Research around the globe suggests that several cytokines are crucial for the progression and development of renal and intestinal fibrosis and associated inflammation. Diabetic nephropathy is a major cause for the increased expression of these cytokines such as TNF-α and interleukins. In a study with 20 type 2 diabetic KKAy mice treated with astragalosides, some bioactive isolates of *Astragalus membranaceus*, it was reported that the compounds could regulate the TGF-β/SMADS signaling pathway by altering the activity or expression of TGF-β1, SMAD2/3, and α-SMA expression [162].

As mentioned earlier, diabetes mellitus is a complex metabolic disorder, and hence, it also affects the liver. Advanced glycation end products (AGEs) have an acute role in the progression and development of diabetic organ dysfunction. Both AGEs and hyperglycemia can induce hepatocyte damage, insulin resistance, and kidney dysfunction [163, 164]. Xu et al. have identified a major active component of a leguminosae plant *Astragali Radix*, namely, calycosin [165]. It can effectively ameliorate hepatocyte dysfunction by inhibiting the accumulation of AGEs. Thus, it can improve the cell viability and can alter the activity of ER-RAGE and GLUT1 signaling pathways [166]. Moreover, the potential antioxidant property of some leguminosae plant-derived active components is critical in ameliorating diabetes and other associated pathological conditions. However, since there are a wide range of factors, other than the discussed ones, involved in the pathogenesis of diabetes mellitus, further studies investigating the intricate molecular mechanism should be done to confirm the efficacy of Leguminosae family plant-derived products against this metabolic disorder.

6.3. Neurodegenerative Disorders

Multiple networks within the body that connect the different parts which synchronize voluntary as well as involuntary actions comprise the nervous system. The central nervous system (CNS) and the peripheral nervous system (PNS) constitute the two main parts and this complex system controls all the workings of the body. The brain and spinal cord constitute the parts of the CNS, while the PNS primarily contains nerves connecting the CNS to the other parts of the body [167]. Many abnormalities in structural, biochemical or electrical or any part of this system can lead to different pathophysiological conditions which are not only restricted to the nervous system but also involve other systems of the body, affecting the body as a whole [168]. The damage to the nervous system leads to a number of diseases all together, termed as neurological disorders. With increasing changes in now-a-day lifestyle, these diseases have become rampant in the society [169]. Drinking, smoking, inadequate sleep, odd working hours, stress, and depression are the biggest contributors to neurological disorders. Interestingly, the above entire ranges of habits result in a common outcome of oxidative stress which acts as the primary triggering factor behind most of the neurological disorders. More than 600 types of neurological disorders with various underlying causes have been reported till date. Genetic disorders, infections, congenital defects, and neuropsychiatric illnesses are factors other than injuries to the brain, spinal cord, and nerve, that also contribute greatly to the pathophysiological conditions in the nervous system [170]. The utmost bulging disorders associated with CNS and PNS include neurodegenerative diseases which further can be classified as movement and related cognitive disorders [171]. Additionally, abnormalities in other organs or systems that interrelate with the nervous system lead to neurological deteriorations like cerebrovascular disorders and autoimmune disorders [172].

In a study involving the pathogenesis of neurodegeneration, it has been shown that dehydroglyasperin C (DGC) derived from Licorice or Liquorice is beneficial against externally induced neuro-inflammation, production of TNF-α, and associated neurodegeneration in BV-2 cells [173]. Exposure to DGC can attenuate the phosphorylation of the key regulators in the MAPK pathway induced by LPS by elevating the expression of MAPK phosphatase 1 (MKP-1) and action of the transcription factor NF-κB [174]. In addition to this, it was also reported that DGC could resist morphological and cytological changes induced by the LPS-containing media in the microglial cells and increase the percentage of microtubule-associated protein 2 positive cells and the synaptophysin level.

In a study of a Chinese herbal medicine Yokukansan, from different legume plant extracts, it has been found to be effective against several neurodegenerative aliments. It has also been proved that Glycyrrhiza (a legume product) is a major active component of yokukansan and it can contribute significantly to its neuroprotective effect. The pathogenesis of glaucoma is still a debatable topic, but various reports suggest that ROS-induced cellular death is critical for this pathophysiological state [175]. An in vitro study with retinal ganglion cells (RGC-5) revealed that among the different active compounds isolated from the Leguminosae plant, *Psoralea corylifolia*, bakuchiol is effective in inhibiting the cell death induced by oxidative stress. It can modulate the intracellular calcium homeostasis and intrinsic apoptotic pathway activated by ROS [176]. Apart from this, the active components from the fenugreek seed were found to be effective in reversal of the symptoms of Parkinson's disease in experimental MPTP-induced mice model. Oral administration of the active component at a dose of 30 mg/kg body weight can improve the motor functioning and does not show any sort of anticholinergic effect or inhibit MAO-B enzyme activity [177].

Another legume plant product, known as puerarin, is also proved to be prophylactic against 6-hydroxydopamine-induced neurotoxicity. It is also found to be effective against Parkinson's disease as it can upregulate the neurotrophic factor derived from glial cells [178]. Apart from this, a study with the neuroblastoma cell SH-SY5Y treated with an ER stress-inducing agent tunicamycin (TM), soy-derived isoflavones protect the cells from apoptosis by interfering the signaling pathway involving immunoglobulin binding protein (BiP), spliced X-box binding protein-1 (Xbp-1), and C/EBP homologous protein (CHOP). These soy-derived phytoestrogens such as genistein and daidzein can also inhibit hyperphosphorylation of tau proteins by downregulating the glycogen synthase kinase 3β (GSK-3β) [179]. In conclusion, it can be inferred that phytochemicals derived from the Leguminosae plant have diverse neuroprotective effects against several neurotoxic and neurodegenerative disorders.

6.4. Osteoporosis

Osteoporosis is a metabolic bone disease due to gradual loss of bone density. Oxidative stress decreases bone formation by reducing the differentiation and survival of osteoblasts. On the other hand, minimum levels of ROS can activate osteoclasts, thereby enhancing bone resorption. Again, the involvement of ROS and its role in the pathogenesis of osteoporosis have been suggested by many clinical reports. Several research reports around the globe suggest that the naturally occurring antioxidant molecules, due to their lower toxicity compared to the other commercially available nutritional supplements, are effective against this degenerative disorder.

Different soy isoflavones have been shown to be effective against postmenopausal bone loss. Out of many, genistein and glycitin showed a remarkable anti-osteoporotic effect. These molecules have been found to induce proliferation and migration in fibroblast cells via TGF-β signaling. The ethanolic extract of *Podocarpium podocarpum* is found to be anti-osteoporotic in ovariectomized (OVX) rats and can effectively maintain different bone resorption markers [180]. Another Fabaceae plant product, 2,4,5-trimethoxyldalbergiquinol (TMDQ), isolated from *Dalbergia odorifera* has been found to facilitate differentiation of the osteoblastic cells and mineralization by modulating the BMP and Wnt/β-catenin pathway [181]. In another study with the hFOB1.19 cells, puerarin has been reported to inhibit glucocorticoid-induced cell death by affecting the pJNK and pAKT-mediated intrinsic apoptotic pathway.

6.5. Obesity

During the last few decades, there has been a significant increase in the prevalence of obesity and it is reaching epidemic proportions in many countries. Obesity has been described as a state of chronic oxidative stress. Furthermore, oxidative stress is reported as the link between obesity and the major associated disorders, such as insulin resistance and hypertension. Replacement of the energy-dense foods with legumes is effective in the prevention and management of obesity and its related disorders as suggested by recent studies. In a report by Abete et al., it was shown that obtaining more than 15% of daily energy intake from protein, i.e., having a hypocaloric legume rich diet for eight weeks, effectively elevates the mitochondrial oxidation. This diet contributes significantly to weight loss when compared with the regular diet containing the same protein content from different protein sources other than legumes. In diet-induced obese mice, administration of the *Parkinsonia aculeate* resists the pathophysiological condition due to insulin resistance-associated oxidative stress by modulating the PPARγ/CuZn-SOD signaling pathway [182]. Soybean and several processed soy products are also experimentally proven to decrease different cardio-metabolic risk and other associated diseases such as diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD) [183].

7. CONSTRAINTS RELATED TO LEGUMES PRODUCTION AND YIELD

Legumes form the major source of dietary proteins and constitute an important part of the vegetarian or vegan diet. Despite their importance, not much attention is being paid to crop improvement of the Leguminosae family plants [22]. Legumes are seeded toward the end of the growing season and are often grown after corn or paddy. They face a number of constraints which are discussed here. First of all, despite some of the plants having short growing seasons; they may be subjected to intermittent or terminal drought. Progressive soil chemical and physical degradation and acid soil conditions may also limit their productivity. There is an urgent need to develop drought tolerant legume plant varieties; parallel to it, an increase in the salinity tolerance is a requirement in many areas. Legumes, such as cowpea, are deeply rooted, and may have reduced leaf size with thickened cuticles to reduce water loss, thereby being more drought-tolerant. In case of less tolerant legumes such as beans, selection can be done on the basis of early maturity, efficiency in the partitioning of nutrients toward reproductive structures, and phenotypic plasticity [184]. Pinto Villa has these characteristics and is now grown in over 90% of the pinto bean area in Mexico.

Depletion of nutrition in soil is also a problem, particularly for small landholders in developing countries, where much grain-legume production occurs. Hydrogen ion concentration per se, aluminum and manganese toxicity, and also phosphorus, molybdenum, or calcium deficiency all contribute to the problem [185]. Other than these constraints, soil acidity affects legume production worldwide. This constraint is likely to grow in the coming years due to processes like natural weathering, acid rain, and nitrogen containing fertilization. The survival, nodulation, and nitrogen fixation of rhizobia in soil are particularly affected by acidic soil conditions. Moreover, pests and diseases offer another major challenge for legume cultivation. Important pathogens include several viruses, fungi-causing root rots, anthracnose, angular leaf spot, bean rust, white mold, and web blight.

The following points elucidate the measures to overcome constraints and increase the yield of legumes: (i) an integrated approach is required for pest management and vector control; (ii) improving agricultural yield by developing improved varieties of seeds; (iii) motivated and focused research must be encouraged for better understanding of the progress of the disease and for identifying molecular markers for development of resistant strain; (iv) cost-effective technologies to aid in increasing yield via combating the natural constrains such as drought; and (v) an initiative should be taken to bridge the gap between farmers and improved technologies as well as the availability of biofertilizers for fields with low nutrient content to increase the yield of legumes by government bodies across the world.

8. ADVERSE EFFECTS DUE TO PRODUCTS FROM LEGUMINOSAE FAMILY PLANTS

Allergies are the major side effects that can arise from consumption of a diet rich in legume products. Immediate hypersensitivity reactions due to legume plant extract/products have been reported by many researchers around the globe. Cross-reactivity is reported in the in vitro systems among legume plants. However, the hypersensitivity reaction varies among individuals and their dietary habits [186]. Legumes, peanuts, and soybean are some of the popular products that belong to Leguminosae family and can also serve as a source of allergens. Pulses such as cajon pea, French bean, horse gram, black gram, and lentils form a part of the common diet in Indians and there are reports of allergic reactions due to these pulses. Green peas, navy beans, dals such as urad, lentil, and gram have shown mild or severe anaphylactic reactions, and some people showed severe gastric and asthmatic symptoms. The allergic proteins in soybean, dal, and peanut have been well-characterized. About 16 fractions have been identified in raw peanuts by crossed radioimmunoelectrophoresis (CRIE) and 8–10 in Bengal gram. SDS-PAGE analyses showed about 32 proteins in peanuts, among which Arah 1, Arah 2, Arah 3 have been identified as major allergens in the Leguminosae plant products [187].

Allergic reactions to peanut and soybean are commonly reported in children and adults, majorly in western countries like the Unites States and European states. A common food allergy in children and adults are peanut allergy and the prevalence of this allergy appears to be increasing. On an average age of 18 months, infants are also susceptible to peanut allergy, although presentations even in adulthood are not uncommon. The presentation of disease at an older age is observed less frequently when people try to introduce this food to their diet or a delayed presentation of peanut allergy due to cross-reactivity with pollens. Although, this allergy has been shown to resolve in a subset of young children whose peanut allergy manifested in infancy but the likelihood of outgrowing an allergy to peanut is far less than it is for milk or egg. Children who had a peanut-specific IgE level $\geq$ 5.0 kU/L or a skin prick test (SPT) response $\geq$ 13 mm at 1 year of age, were unlikely to outgrow the allergy by the age of 4 years. Peanut-specific higher IgE levels have not only been associated with more persistent peanut allergy but also with more severe allergic reactions upon ingestion of peanut. The majority of peanut allergic children who become tolerant to this allergy, will do so early in life but there have been cases of resolution in adulthood and patients may benefit from long-term follow-up [188, 189].

Soybean is used across the globe as a part of the regular diet due to its high nutritional values. However, they also elicit allergic reactions in susceptible individuals. Even oil from peanut and soybean, other than refined ones, can stimulate allergic reactions.

Recently, soybean has been identified as an aeroallergen, capable of inducing asthma. Among the soy proteins, vicilin is an important soy allergen and four other protein fractions have also been identified as allergens [190].

Chickpea also constitutes a common part of the staple diet and is mostly used as a thickening agent. Among the pulses, chickpea is reported to be a potential allergen. A chickpea hypersensitivity study was undertaken and was diagnosed by skin tests, ELISA, and double-blind placebo-controlled food challenges (DBPCFCS) in 59 patients, and it was found that chickpea is an important allergen for IgE-mediated hypersensitive reactions ranging from rhinitis to anaphylaxis. Lupin, consisting of approximately 450 species, is a legume belonging to the family of Leguminosae. Since ancient times, it has been used as human food and animal feed. Allergic reactions to lupin have emerged as an issue following its introduction in processed foods in the late 1990s in the Europe [191].

Food legumes like some oilseeds, peas, and beans form important sources of protein and calories for a large section of the world's population. A major challenging scientific problem associated with the consumption of such foods is elimination of flatulence. The consumption of soybeans may provide a number of beneficial effects due to their phytochemical constituents, but a major challenge is flatulence that remains associated with high soy diet. The extent and severity exhibit variability among individuals depending on their dietary habits. Several studies have shown that the major cause of soybean flatulence is the oligosaccharides, including verbascose, stachyose, and raffinose. Improper digestion of these oligosaccharides and further fermentation by intestinal microflora cause the formation of gas and thus flatulence [192]. The lack of α-galactosidases in the intestines leads to the escape of these oligosaccharides from the digestive process and they are then finally fermented by active microflora in the large intestine to form high levels of rectal gas, primarily hydrogen and carbon dioxide. Some methods like soaking, fermentation, enzymatic hydrolysis, and germination can also be used to eliminate oligosaccharides and thereby reduce the occurrence of flatulence in the daily dietary uptake of soy products. The ejection of rectal gas may accompany abdominal pain, nausea, cramps, diarrhea, increased peristalsis, borborygmus, and social discomfort [193].

9. CONCLUSION

In the present-day scenario, increase in the percentage of unsustainable human activities lead to complex pathophysiological conditions. In the recent years, contemporary chemically synthesized drugs have proven to be mostly ineffective and unsafe due to their various side effects in the clinical management of several anomalous conditions including the diseases discussed in this article. The researchers around the globe are proposing an alternative to this––different phytogenic bioactive compounds [84, 194–197]. Among them, the several plant-derive compounds like polyphenols, bioflavonoids, and phytoestrogens are gaining more attention as they have proven to be fit for human consumption and appropriate in the management of the diverse diseased conditions. As discussed in this article, phytochemicals obtained from leguminous plants are easily available in our diet and are a cost-effective option in the current world scenario. This article compiles the different protective effects of various phytochemicals obtained from leguminous plants in numerous pathophysiological states. As discussed earlier, these phytochemicals have the potential to protect against various diseased conditions. However, the adverse effects of flatulence and allergies need to be addressed. The prophylactic roles are too numerous than their side effects; therefore, leguminous plants are still a rich and promising source of oxidative stress-combatting molecules.

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