# Health Benefits of Isoflavones Found Exclusively of Plants of the Fabaceae Family



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# Chapter 22
# Health Benefits of Isoflavones Found Exclusively of Plants of the Fabaceae Family

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## 22.1 Introduction

The Fabaceae or Leguminosae family commonly known as the legume, pea, or bean family, are a large and economically important family of flowering plants. It includes a wide range of trees, shrubs and herbaceous plants, perennials or annuals, easily recognized by their fruits (legume) and their compound, stipulated

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leaves. The group, with 730 genera and over 19,400 species, is widely distributed and is the third-largest plant family in terms of number of species behind only to the Orchidaceae and Asteraceae (Judd et al. 2002). The largest genera are Astragalus (over 2400 species), Acacia (over 950 species), Indigofera (around 700 species), Crotalaria (around 700 species), and Mimosa (around 500 species), which contain around 9.4% of all flowering plant species (Magalion and Sanderson 2001). The family itself is the most common family found in tropical rainforests and in dry forests in American and Africa. It has traditionally been divided into three subfamilies: Caesalpinioideae, Mimosoideae, and Papilionoideae (Lewis et al. 2005) and includes almost all the major pulses like mung, urad, pigeon pea, moth bean, cow Pea, adzuki bean, etc. The plant species under Fabaceae family with medicinal importance includes Cassia, Senna, Mimosa, Crotoleria etc. which

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are being extensively used by the therapeutic drug industries, with high demands in the market of herbal medicine.

Recent molecular and morphological evidence supports the fact that the Fabaceae is a single monophyletic family (Lewis et al. 2005). The fact has been supported not only by the degree of interrelation shown by different groups within the family, but also by all the recent phylogenetic studies based on DNA sequences (Kajita et al. 2001). These studies confirm Leguminosae as a monophyletic group with close relation to Polygonaceae, Surianaceae and Quillajaceae families. Many cereals, several fruits and tropical roots of Leguminosae family have been a staple human food for millennia and their use is intertwined with human evolution (Burkart 1987). A number are important agricultural and food plants, including *Glycine max* (soybean), Phaseolus (beans), *Pisum sativum* (pea), *Cicer arietinum* (chickpeas), *Medicago sativa* (alfalfa), *Arachis hypogaea* (peanut), *Ceratonia siliqua* (carob), and *Glycyrrhiza glabra* (liquorice). A number of species are also weedy pests in different parts of the world, including: *Cytisus scoparius* (broom), *Ulex europaeus* (gorse), *Pueraria lobata* (kudzu), and a number of *Lupinus* species (Sprent 2009; Wojciechowski et al. 2004).

## 22.2 Isoflavones: Biosynthesis and Mode of Action

Isoflavones are group of secondary metabolite formed by a symbiotic relationship with the rhizobium bacteria and the defence responses of leguminous plants (Yu et al. 2000). Isoflavons are synthesized as part of the phenylpropanoid pathway, the same biosynthetic pathway of flavonoid biosynthesis (Barnes 2010). Phenylalanine converts 4-hydroxycinnamoyl CoA by reaction with malonyl CoA. Chalcone synthase catalyzes the reaction of this intermediate to convert to 4,2,4′,6′-tetrahydrozychalcon (naringenin chalcone) and the combined enzyme reaction of chalcon synthase and chalcone reductase convert this intermediate to 4,2′,4′-trihydrozychalcone (isoliquiritigenin). Then, chalcone isomerase catalyzes the ring closure of the heterocyclic ring to form 7,4′-dihydrozyflavone (liquiritigenin) and 5,7,4′-trihydroxyflavone (naringenin). The B-ring is moved from the 2-position to 3-position by isoflavone synthase. Isoflavone dehydratase removed water to generate the 2,3-double bond in the heterocyclinc ring. The products generated by this reaction were daidzein (7,4′-dihydroxyisoflavone) and genistein (5,7,4′-trihydroxy isoflavone).

According to the xenohormesis theory, plants synthesize phytochemicals to withstand and adapt under stress (Table 22.1). Indeed, isoflavone biosynthesis depend on the environmental conditions in which the plant grows and is stimulated by stress. The stress-induced plant compounds have the ability to upregulate stress adaptive pathways in animals and humans. In the body, modulating pathways mediated by estrogen receptors (ERs) or various key enzymes involved in cellular signalling or metabolism and antioxidant potential exercise the precise biological effects of isoflavones (Cederroth and Nef 2009).

**Table 22.1** List of Selected Plants with Reported Isoflavone Content

| S/N | Scientific name | Local name | Habit | Part(s) used | Uses | References |
|---|---|---|---|---|---|---|
| 1. | *Abrus precatorius* L. | Kuch | Climber | Seed, root | Paralysis, sciatica, stiffness of the shoulder joint, white leprosy, stimulant. | Rahman et al. (2015) and Saxena and Sharma (1999) |
| 2. | *Acacia catechu* (L. f.) Willd | Khair | Tree | Bark | Astringent, anthelmintic, antidysentery, antipyretic, cures itching, inflammations, sore throat, bronchitis, indigestion, ulcers, boils, leukoderma, psoriasis, leprosy and elephantiasis, strengthens the teeth. | Rahman et al. (2015) |
| 3. | *Acacia nilotica* (L.) Willd. ex Delile | Babla | Tree | Leaf, pods, flower | Astringent, tonic to the liver and brain, antipyretic, leukoderma, gonorrhoea, strangury, diarrhoea, cystitis, vaginitis, dysentery, ophthalmia, cough and insanity. | Rahman et al. (2015) |
| 4. | *Albizia lebbek* (L.) Benth | Sirish | Tree | Leaf, seed | Ophthalmia, asthma, astringent, tonic to the brain, gonorrhoea, tubercular glands, leukoderma and leprosy. | Rahman et al. (2015) |
| 5. | *Albizia procera* (Roxb.) Benth | Koroi | Tree | Leaf, bark | Insecticidal, ulcer, worms and scabies. | Rahman et al. (2015) and Rastogi and Mehrotra (1993) |
| 6. | *Bauhinia acuminata* L. | Kanchan | Tree | Leaf, bark | Biliousness, bladder stone, asthma and leprosy. | Rahman et al. (2015) and Yoshikawa (2000) |
| 7. | *Butea monosperma* (Lam.) Taub. | Palash | Tree | Bark | Aphrodisiac, laxative, anthelmintic, dysentery, piles, cold, cough, astringent, diarrhoea and stomatitis. | Rahman et al. (2015) and Velis et al. (2008) |

(continued)

**Table 22.1** (continued)

| S/N | Scientific name | Local name | Habit | Part(s) used | Uses | References |
|---|---|---|---|---|---|---|
| 8. | *Cajanus cajan* (L.) Millsp. | Arhar | Shrub | Leaf, root | Diabetes and jaundice. | Rahman et al. (2015) and Primiani and Pujiati (2016) |
| 9. | *Caesalpinia bondus* L. | Nata | Shrub | Seed | Kidney disease and blood pressure. | Rahman et al. (2015) and Srinivas et al. (2003) |
| 10. | *Caesalpinia pulcherrima* (L.) Sw. | Choto krisnachura | Tree | Whole plant, root, flower, wood | Tonic, stimulant, astringent, cholera, purgative, abortifacient, febrifuge, bronchitis, asthma, malarial fever, intestinal worms, coughs, chronic catarrh, emmenagogue, diarrhoea, dysentery and internally in skin diseases. | Rahman et al. (2015) and Srinivas et al. (2003) |
| 11. | *Cassia fistula* L. | Badarlathi | Tree | Leaf, root | Burning sensation, leprosy, syphilis and malaria. | Rahman et al. (2015) and Sartorelli et al. (2009) |
| 12. | *Clitoria ternatea* Linn. | Aparajita | Climber | Bark, leaf, flower | Irritation of the bladder and urethra, earaches and cough of children. | Rahman et al. (2015), Yanishlieva et al. (2001) and Chang et al. (2002) |
| 13. | *Crotalaria alata* D. Don. | Jhunjhuni | Herb | Seed | Rheumatism. | Rahman et al. (2015) and Radwan et al. (2008) |
| 14. | *Dalbergia sissoo* Roxb. | Sissoo | Tree | Wood, leaf | Abscess, astringent, haemorrhages, epistaxis, menorrhagia, bleeding piles and acute stage of gonorrhoea. | Rahman et al. (2015) and Sarg et al. (1999) |

(continued)

**Table 22.1** (continued)

| S/N | Scientific name | Local name | Habit | Part(s) used | Uses | References |
|---|---|---|---|---|---|---|
| 15. | *Desmodium gangeticum* (L.) DC. | Chalani | Herb | Root | Alterative, tonic, anthelmintic, aphrodisiac, astringent to the bowels, typhoid, fever, piles, asthma, bronchitis, dysentery, diarrhoea, biliousness, cough, chronic affections of the chest and lungs and whooping cough. | Rahman et al. (2015) and Grynkiewicz et al. (2005) |
| 16. | *Desmodium triflorum* (L.) DC. | Kodalia | | | Antioxidant and antiproliferative activities | Rahman et al. (2015) |
| 17. | *Erythrina variegata* L. | Madar | Herb | Leaf, root | Blindness, eye diseases, sores, whitlow, spleen complaints, stomach trouble, colic, diarrhoea, menorrhagia, breast pain, galactagogue, laxative, dysentery, wounds, abscesses, carminative, tonic, diuretic, cough, asthma and bilious complaints. | Rahman et al. (2015) and Sato et al. (2002) |
| 18. | *Lablab purpureus* (L.) sweet | Sim | Climber | Leaf | Fresh leaves pounded and mixed with lime are rubbed over ringworms to cure. | Rahman et al. (2015) |
| 19. | *Melilotus indica* (L.) All. | Banmethi | Herb | Root | The roots of this plant and *Amaranthus spinosus* are crushed together and taken with water, to stop bleeding through nose and mouth. | Rahman et al. (2015) |
| 20. | *Mimosa pudica* L. | Ljjabati | Climber | Root | Fever and snake-bite. | Rahman et al. (2015) |
| 21. | *Mimosa diplotricha* C. Wright ex Sauv. | Sadalajjabati | Herb | Leaf | Skin diseases. | Rahman et al. (2015) |

(continued)

**Table 22.1** (continued)

| S/N | Scientific name | Local name | Habit | Part(s) used | Uses | References |
|---|---|---|---|---|---|---|
| 22. | *Pisum sativum* L. | Motor | Herb | Seed | Refrigerant, appetizer, fattening, laxative, alleviative of bile, phlegm, burning of the skin and, emollient. | Rahman et al. (2015) and Pudenz et al. (2014) |
| 23 | *Pithocelobium dulce* (Roxb.) Benth | Gilapifol | Tree | Leaf | Febrifuge and enema, Saponins showed significant activity against carrageenin-induced oedema and formaldehyde-induced arthritis. Ethanolic extract of the leaf possesses strong antifungal and moderate antibacterial properties. | Rahman et al. (2015) |
| 24. | *Saraca asoka* (Roxb.) de Wilde | Asoke | Tree | Bark, leaf, flower | Irregular menstruation, blood-purifying properties, stomach ache, excellent uterine tonic, haemorrhagic dysentery. | Rahman et al. (2015) |
| 25. | *Senna sophera* L. | Kalkasundha | Herb | Leaf, root | Dyspepsia. | Rahman et al. (2015) |
| 26. | *Senna alata* (L.) Roxb. | Dadmardan | Shrub | Leaf | Eczema | Rahman et al. (2015) and Rahman et al. (2015) |
| 27. | *Senna occidentalis* Roxb. | Boro kolkeshundha | Shrub | Root | The root is made into a paste and given to nursing women for purification of the milk. | Rahman et al. (2015) |
| 28. | *Senna tora* (L.) Roxb. | Chakunda | Herb | Leaf | Leaves and seeds are used as remedy for ring worm, skin disease and asthma. | Rahman et al. (2015) |
| 29. | *Tamarindus indica* L. | Tentul | Tree | Fruit, leaf, bark | Burning sensation, heart disease, astringent and tonic, asthma, amenorrhea, fever, diarrhoea and topically for loss of sensation in paralysis. | Rahman et al. (2015), Nandave et al. (2005) and Sisa et al. (2010) |

(continued)

**Table 22.1** (continued)

| S/N | Scientific name | Local name | Habit | Part(s) used | Uses | References |
|---|---|---|---|---|---|---|
| 30. | *Uraria picta* (Jacq.) DC. | Sonkarjata | Herb | Whole plant, leaf, root, pods | Heart trouble, fractured bone, aphrodisiac properties, cough, chills and fevers, antiseptic, gonorrhoea, pods are useful in sore-mouth of children. Roots and leaves are used for typhoid and tetanus. | Rahman et al. (2015) |
| 31. | *Vigna mungo* (L.) Hepper | Maskalay | Herb | Seed | Laxative, aphrodisiac, tonic, appetizer, diuretic, galactagogue, styptic, piles, asthma, leukoderma, scabies, gonorrhoea, pains, epistaxis, paralysis, rheumatism and affections of the nervous system, liver and cough. | Rahman et al. (2015) |

Flavonoids are one of the most representative classes of secondary plant metabolism. They are divided into two main groups: the flavonoids and isoflavonoids. Flavonoids mixed biosynthesis products, include a basic molecular skeleton with fifteen carbon atoms ($C_6C_3C_6$). The isoflavones are structurally distinct from the other flavonoid classes because they contain a C15 skeleton based on 1,2-diphenylpropane, while the other classes have 1,3-diphenylpropane. Isoflavones (IFs) are yellow pigments derived from 3-phenyl-benzopyrone (3-phenyl-chromone) structure. They are found in plants, mostly as biologically inactive glycosides, namely 7-O-β-D-glycosides, 6″-O-acetyl-7-O-β-D-glucosides, and 6″-O-malonyl-7-O-β-D-glycosides (Tsao 2010; Bolca 2014). After ingestion, glycosides are not bioavailable to be absorbed through enterocytes (Setchell et al. 2002). They are hydrolyzed into bioactive aglycones by both intestinal mucosa and bacterial β-glucosidases from the gut microbiota. Only these forms are absorbed into systemic circulation directly or after subsequent metabolism in the bowel by intestinal bacteria (Setchell et al. 2002). Soybeans incorporate predominantly genistin, daidzin, and glycitin as inactive glycosides, which are hydrolyzed into their corresponding biologically active aglycones: genistein, daidzein (Fig. 22.1), and glycitein. Other isoflavones observed in legumes are ononin and sissotrin, with their aglycones, formononetin and biochanin A, respectively.

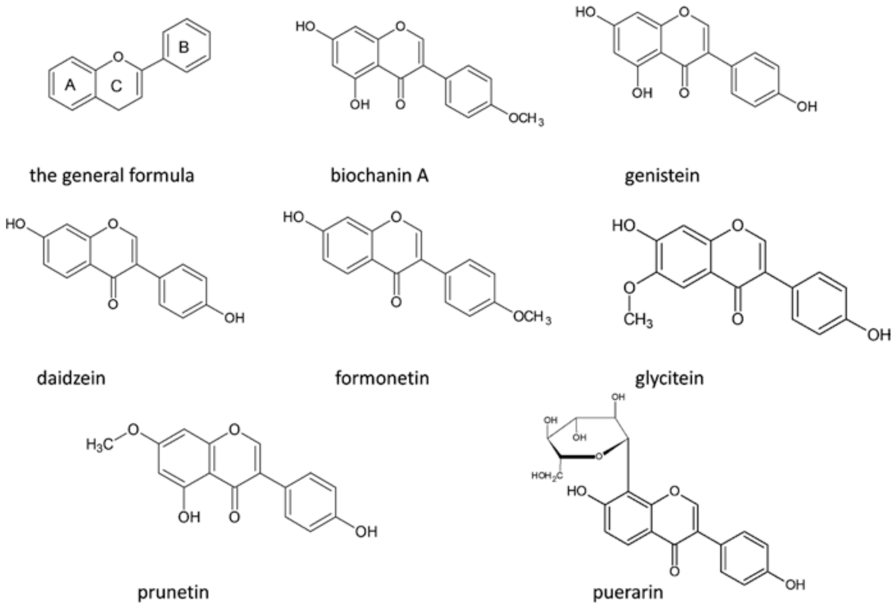


**Fig. 22.1** The structural formulas of some of the isoflavonoids

## 22.3 Flavonoids and Plant Pathogen Resistance

The role of flavonoids in plant defence against pathogens, herbivores, and environmental stress are reviewed and their significant contribution to plant resistance is documented (Lu *et al.* 2017; Treutter 2005). The table below (Table 22.2) highlight several flavonoid compounds having anti-pathogenic activities found in plant organisms.

## 22.4 Isoflavones: Role in Human Health

Unlike the adverse effect of phytoestrogens, isoflavones has established positive role in human healthcare and several researchers investigated the beneficial effects of this important group of bioactive compounds in this regard.

**Table 22.2** List of flavonoid compounds having anti-pathogenic activities found in plant organisms

| Plants | Antimicrobial compound | Pathogen | References |
|---|---|---|---|
| *Dianthus caryophyllus* | Flavonol triglycoside of kaempferide | *Fusarium oxysporum* | Curir et al. (2005) |
| *Dianthus caryophyllus* | Kaempferol-O-rutinoside, Kaempferol-3-O-b-D-glucopyranosyl | *Fusarium oxysporum* | Galeotti et al. (2008) |
| *Linum usitatissimum* | Isoorientin, isovitexin, vitexin | *Fusarium culmorum* | Mierziak et al. (2014) |
| *Triticum L. cv. Roblin* | Flavonoids | *Fusarium graminearum* | Ravensdale et al. (2014) |
| *Lotus garcinii* | Catechin, epicatechin, rutin | *Fusarium graminearum* | Girardi et al. (2014) |
| *Hordeumvulgare* | Naringenin, kaempferol | *Gibberella zeae* | Bollina et al. (2010) |
| *Mariscus psilostachys* | Chalcones | *Cladosporium cucumerinum* | Gafner et al. (1996) |
| *Arabidopsis thaliana* | Quercetin | *Neurospora crassa* | Parvez et al. (2004) |
| *Eucalyptus globules* | Flavonols | *Cytonaema* sp. | Eyles et al. (2003) |
| *Cicer bijugum* | Isoflavonoids | *Botrytis cinerea* | Stevenson and Haware (1999) |
| *Medicago truncatula* | Isoflavone | *Erysiphepisi* | Foster et al. (2007) |
| *Vitis vinifera* | Quercetin-3-O-glucoside | *Plasmopara viticola* | Ali et al. (2012) |
| *Austrian pine* | Flavonoids | *Diplodia pinea* | Sherwood and Bonello (2013) |
| *Glycine max* | Isoflavone | *Phytophthora sojae* | Subramanian et al. (2005) |
| *Solanum tuberosum* | Glucosylated forms of flavonoids | *Erwinia carotovora* | Velasco et al. (2013) |
| *Oryza sativa* | Naringenin, kaempferol, quercetin, hydroxyquercetin | *Xanthomonas oryzae* pv. *oryzae, Pyricularia oryzae* | Song et al. (2013) |
| *Lycopersicon esculentum* | Flavonoids | *Pseudomonas syringae* | Vargas et al. (2013) |
| *Citrus sinensis* | Flavonoid glycosides, polymethoxylated flavones | *Candidatus liberibacter* | Hijaz et al. (2013) |

## *22.4.1 Bone Health and Metabolism*

### 22.4.1.1 Bone Health

Isoflavones exerts estrogen-like effect on bone by binding to ER-β and thus are expected to have positive beneficial effects for bone health including osteoporosis. *In vitro* and animal studies involving isoflavones and bone health suggest a positive relationship between isoflavones and positive action on both osteoblasts and osteoclasts. Through stimulating bone formation and inhibiting bone resorption, isoflavones can maintain bone health. Human studies, including observational and clinical trial studies also support favourable effects of isoflavones showing the results such as increasing bone mineral density and bone mechanical strength, and inhibiting bone turnover in postmenopausal women (Atmaca et al. 2008). Ingestion of isoflavones (more than 90 mg/day of isoflavones) at least 6 months has a significant effect for increasing spine bone mineral density in meta-analyses of randomized controlled trials however the effects on hip and leg bones are controversial (Taku et al. 2010). Long term safety and efficacy for isoflavones ingestion is needed to be confirmed.

#### 22.4.1.2 Bone Metabolism

Bones having increased calcium retention are due to isoflavones. So, increasing bone mineral density. Both genistein and daidzein are effective in preventing bone loss, but daidzein is more potent of these two compounds. Zn, Mn and Cu are essential trace elements needed for optimal formation of bone matrix and bone mineralization. These elements act as cofactors for some specific enzyme. For example, Zn acts as the component of the ALP, which is involved in the formation of bone mineral matrix, and deficiency of Zn causes skeletal defects.

### *22.4.2 Beneficial Effects in Menopausal Women*

Isoflavones helps reinforce estrogenic effect after endocrine fall in estrogen levels through binding to ER-α which then helps to reduce estrogen-related cancer risk. Through binding to ER-β, isoflavones induce estrogen-like effect and thus show positive health effects after menopause. In postmenopausal syndrome with hot flushes and night sweat, isoflavones prescription can decrease the symptoms of menopause (Setchell and Cassidy 1999). Dietary soy products have slightly and modestly reduced climacteric vasomotor relative to placebo (Bolanos et al. 2010).

### *22.4.3 Reduction in Cancer Risk*

*In vitro* and animal studies has shown that isoflavones can reduce cancer risk through antioxidant and anti-tumorogenic effect, such as blocking ER-α protein and stopping carcinogenesis pathway through inhibiting PTK, tumor cell growth by suppressing DNA replication and various growth factors and controlling enzyme activities on the signal transduction pathway of carcinogenesis. Epidemiological studies also show that the soy isoflavones may be associated with a reduction in cancer risk. Soy intakes yield a reduced risk for prostate cancer and breast cancer in recent meta-analyses, among Asian population, although the dose-response relationship is not clear (Qin et al. 2006; Yan and Spitznagel 2009; Dong and Qin 2011). However, the protective effect of soy isoflavones is not significantly found among non-Asian populations who soybeans and soy-related products intake is not frequent (Yan and Spitznagel 2009; Dong and Qin 2011). After stratification for fermentation, non-fermented soy is only a significant preventive effect for breast cancer (Dong and Qin 2011). Soy food intake was associated with not only prevention of breast cancer, but also longer survival and low recurrence among breast cancer patients (Zhu et al. 2011; Kang et al. 2012; Zhang et al. 2012).

The effect of isoflavones for gastric cancer is more complicated and it depends on food processing. Both Korean and Japanese populations have high incidence rates of gastric cancer and frequently eaten a wide variable soy food. In recent meta-analyses, among Korean and Japanese population, non-fermented soy foods show a protective effect for gastric cancer, whereas fermented soy foods present no effect in reducing risk for gastric cancer (Kim et al. 2011). Fermented soy foods, including fermented soy sauce and soybean pastes such as Doenjang and miso, which Korean and Japanese are used to add for making foods with high salt content, and therefore fermented soy foods can be associated with higher risk of gastric cancer due to effect and high salt and N-nitroso compounds. There are few human studies using blood concentrations of isoflavones. In Korean study, isoflavones, including genistein, daidzein and equol have an effect of reducing gastric cancer risk, and the higher concentration of three isoflavones is much lower to facilitate gastric cancer risk (Ko et al. 2010). This protective effect against gastric cancer can be explained as an anti-inflammatory, anti-tumorogenic, and anti-oxidative effect of isoflavones. Although, the effect of isoflavones for other cancer prevention has little compelling evidences up to date, a Japanese recent study using a nested case-control reports an inverse effect for lung cancer (Shimazu et al. 2011) and possible preventive effects of isoflavones for other cancers are expected to be released in future studies.

### *22.4.4 Breast Cancer Prevention*

Estrogen is known to induce breast cancer progression, and interventions, such as dietary modifications, that block or reduce estrogen production are likely to result in favourable prognoses for breast cancer patients. A population-based, prospective study confirmed that frequent isoflavone consumption was inversely associated with the risk of breast cancer (Yamamoto et al. 2003). In another study, researchers found that soy isoflavones did not have estrogenic effects in humans and concluded that such a diet may be safe for breast cancer survivors (Fritz et al. 2013), chemoprotective and can prevent recurrence in breast cancer patients. Numerous other plants of the Fabaceae family have been reported to possess anticancer activities. For instance, one study by Arul et al. (2018) demonstrated that the ethanolic extracts of *Pisum sativum* seeds exhibited cytotoxic activity against human breast adenocarcinoma

(MCF-7) cell lines using the MTT assay. The maximum percentage of growth inhibition was 75.1 ± 7.78%, which was obtained at 6 mg/ml concentration.

### 22.4.5 Anti-diabetic Effect

After menopause, women's glucose tolerance capacities deteriorate and accumulate central fat. As a consequence of these menopausal changes, many menopausal women have an experience in insulin resistance. Although some epidemiological and clinical trial studies have reported that isoflavones has a beneficial effect on insulin sensitivity and glucose metabolism, it is consistent in that isoflavones has slight decreasing insulin resistance observed after menopause. Recent meta-analysis of randomized clinical trials supports the weak effect of isoflavones for diabetes and shows no sufficient evidence in improving glycaemic condition (Ricci et al. 2010). Despite the limited evidences, fermented soy products may have better effects in preventing the progression of type 2 diabetes relative to nonfermented soy products (Kwon et al. 2010). In normoglycemic women, isoflavones is expected to have an association with reduced insulin resistance. In summary, the effect of isoflavones as a treatment medicine for diabetes has no compelling evidences, however, they seem to have a mild effect in preventing diabetes through reducing insulin resistance.

### 22.4.6 Antiaging Effects of Isoflavones

Red clover extract which is rich in isoflavones mainly, formonetin and biochanin A exerts a higher affinity for liposome formation in comparison to genistein and daidzein. Liposome-incorporated red clover extract resulted in a final product with significant antioxidant action as well as additional benefits in aging prevention (Klejdus et al. 2001; Kanouni et al. 2002).

Soy isoflavones demonstrated UVB protective effects due to their antioxidant activities (Chiang et al. 2007). In addition, soy isoflavone extract inhibited UVB-induced keratinocyte death and suppressed UVB-induced intracellular $H_2O_2$ release, decreased the epidermal thickness and inhibited COX-2 and proliferating cell nuclear antigen (PCNA) expression. UVB-triggered activation of p38, c-Jun N-terminal kinase (JNK) and extracellular signal regulated kinase (ERK1/2) which were inhibited by treatment with a soy isoflavone extract (Chiang et al. 2007; Chiu et al. 2009; Assefa et al. 2005).

Huang et al. (2010) evaluated the protective effects of soy isoflavone extract fraction 3 from soybean cake that contains the aglycone group (daidzein, genistein and glycitein) and acetylglucoside group (acetyldaidzin, acetylgenistin and acetylglycitin) on UVB-induced damage. The fraction inhibit UVB-induced death of human keratinocytes and reduce the level of desquamation, transepidermal water loss, erythema and epidermal thickness in mouse skin. Furthermore, topical application of the fraction 3 increased the activity of catalase and suppressed cyclooxygenase-2 (COX-2) and proliferating cell nuclear antigen (PCNA) expression in mice exposed to UVB.

Kim et al. (2004) investigated the anti-aging effects of dietary intake of isoflavones on photoaged (UV-irradiated) hairless female mouse skin for 4 weeks. The isoflavone oral administration resulted in better appearance and less wrinkling of the skin and higher amount of collagen deposit. The isoflavones also suppressed the UV-increased metalloproteinases (MMP-1) expression.

Isoflavones bind to estrogen receptors preferentially to 24 and transactivate 25 estrogen receptor-β that is the predominant receptor in the skin (Thornton et al. 2003a, b). In addition, isoflavones also have an effect on the skin, which is independent of estrogen receptor binding. Genistein, the soybean isoflavone is suggested to prevent photoaging through inhibiting the UV-induced epidermal growth factor receptor tyrosine kinase activity and its effect on several other signal transduction pathways in human (Kang et al. 2003). Genistein prevented UV-B irradiation induced skin damage when applied to the human reconstituted skin (Moore et al. 2006). Subcutaneous administration of genistein aglycone in mature ovariectomized rats has shown to improve skin (wound) healing and tensile strength with a greater effect than raloxifene and estradiol (Marini et al. 2010).

Equol, an isoflavandiol estrogen metabolized from daidzein, contains a chiral carbon and exists as enantiomers, S- and R- equol, where both enantiomers can specifically bind to 5α- dihydrotestosterone (DHT) stimulating androgen receptors (ARs) in the keratinocytes of the epidermis/dermis, fibroblasts, and sebocytes. Equol ability to stimulate collagen was tested on human dermal monolayer fibroblasts, where collagen deposition was quantified by collagen type 1 C-terminal peptide by ELISA assays. Equol effect on cell viability was similar to that of 17β-estradiol as shown by MTT assay. Equol could stimulate collagen deposition at different concentrations at significantly higher levels compared to 17β-estradiol (Lephart et al. 2005). Equol, also protects against UV induced skin damage (Widyarini et al. 2005).

Soy isoflavone emulsion could rejuvenate the structure of mature skin by topical application in a placebo-controlled study, through increasing the number of dermal papillae after 2 weeks, since flattening of the dermal-epidermal junction is most considered as important reproducible change in skin aging (Südel et al. 2005).

In a Brazilian study, estrogen and isoflavones were tested on 35 postmenopausal women for 24 weeks of topical application. Both drugs improved the histomorphometrical parameters; but estrogen was more effective than isoflavones (Moraes et al. 2009). Isoflavones can be absorbed effectively through the skin and thus, can exert good protection against photoaging and photodamage (Huang et al. 2008). In fact, Minghetti et al. 2006 suggested that topical administration could lead to circulating isoflavone levels sufficiently to have systemic effects. Bifidobacterium-fermented soy milk (BFS) extract containing genistein and daidzein was tested on the skin of hairless mice by topical application for 6 weeks and it improved the elasticity and viscoelasticity of mouse skin, increased hyaluronic acid content and increased hydration and thickening of the skin. Hyaluronic acid is a major component of skin where it is involved in tissue repair. Topical application of a gel formula containing 10% BFS to the human forearm for 3 months also improved skin elasticity (Miyazaki et al. 2004).

In a pilot study performed by Draelos et al. (2007), two groups of 20 healthy postmenopausal women were each instructed to consume their usual diet with or without 20 g/d of an isoflavone-rich soy protein. There were statistically significant improvements in facial-skin wrinkling, discoloration and overall appearance in the supplement group.

Treatment of 30 postmenopausal women with 100 mg/d of an isoflavones-rich soy extract for 6 months led to an increase in the epidermal thickness in 23 women and collagen amount in the dermis in 25 women with a reduction in the papillary index in 21 women. Further, the number of elastic fibres and dermal blood vessels increased in 22 and 21 women, respectively (Accorsi-Neto et al. 2009).

A study was conducted on 26 premenopausal Japanese women, they were maintained on supplements that provided 40 mg/d isoflavones for 3 months, this led to a statistically significant decrease in fine wrinkles with an increase in skin elasticity, especially in week 8, compared to the placebo group (Stevenson and Thornton 2007).

### *22.4.7 Cardiovascular Health*

Isoflavones binding to ER-β at low endocrine estrogen level, have an agonist effect on estrogen in the cardiovascular system. Also, isoflavones can directly relax vessels by possibly enhancing the promotion of prostacyclin release and anti-inflammatory action and indirectly reduce plaques in vessels by inhibiting collagen-induced aggregation and platelet activation, although the clear mechanisms are not known (Cano et al. 2010). Physiologically, isoflavones are related in reducing lipid profiles such as low-density lipoprotein against global oxidation in endothelial cells. However, the role in total cholesterol and triglycerides is controversial (Cano et al. 2010). In the view of nutrition, many soy products contain high content of polyunsaturated fats, fibre, vitamins, and minerals and low content of saturated fat. Based on these mechanisms and nutritional point of view, isoflavones are beneficial to cardiovascular health by reducing cardiovascular burden in human. Recent meta-analyses using clinical trials to support the cardiovascular healthy role of isoflavones, reveals that isoflavones significantly increase flow-mediated dilatation in vessels and decrease arterial stiffness relative to placebos although heterogeneity across the studies was presented (Li et al. 2010; Pase et al. 2011).

Several phytochemicals that are extracted from the plants of the *Fabaceae* family exhibited exclusive cardiovascular effects. Randrianarivo et al. (2014) evaluated the toxic effects of extracts obtained from the seeds of nine different plants that belongs to the *Fabaceae* family of Madagascar region. It has been reported that all the seed extracts possess large quantities of alkaloids and saponins, where only the extracts of *A. masikororum* and *A. viridis* triggers a positive inotrope effect towards isolated auricles followed by complete atrial arrhythmia via progressive inhibition of contraction (Randrianarivo et al. 2014). Similarly, Atchibri et al. (2010) examined the bioactive extracts of *Phaseolus vulgaris* seeds and revealed that saponins, flavonoids, glycosides, alkaloids, steroids, terpenoids and tannins are present as the significant functional phytochemicals. Further, the study emphasized that the phytochemicals present in these seed extracts lead to their unique antioxidant, anticarcinogenic, antimutagenic and antihyperglycemic effects which will be useful in reducing cardiovascular complications (Al et al. 2010). Likewise, aqueous leaf extract of *Acacia tortilis* was evaluated by injecting them into rats for 7 days. The results revealed that the extracts contain flavonones, flavones, flavonols, coumarins, leucoanthocynanins, anthacyanins, tannins, tertiary and quaternary alkaloids. These phytochemicals help in reducing blood glucose, serum total cholesterol and low density lipoprotein level which will eventually reduce diabetes related cardiovascular complications such as myocardial infarction (Alharbi and Azmat 2011). Apart from other phytochemicals, the presence of isoflavone has been reported to elevate the cardiovascular effects of plant extracts from *Fabaceae* family. Isoflavones are the phytocompounds that belong to the group of flavonoids, which are present in most of the *Fabaceae* plants (Peluso 2006). Thus, Table 22.3 summarizes important isoflavones extracted from different parts of Fabaceae plants that exhibited enhanced cardiovascular effects.

### 22.4.8 Antimicrobial Activities of Plants of the Family Fabaceae: A Summary of Major Research Findings from 2009 to 2019

Arote et al. (2009), validated the antimicrobial effects of methanol extracts, petroleum ether extract, ethyl acetate extract and chloroform extract obtained from the leaves of *Pongamia pinnata* Linn, a species of tree in the pea family. The antibacterial activity was carried out using disc diffusion method against some enteric pathogenic bacteria which were *Salmonella typhimurium, Staphylococcus aureus, Enterobacter aerogenes, Klebsiella pneumonia, Proteus vulgaris, Staphylococcus epidermidis, Pseudomonas aeruginosa, and Bacillus subtilis.* The result revealed that the methanolic extract exhibited the strongest antimicrobial activity when compared to other extract used. The high antimicrobial activity might be linked to the presence of saponins, tannins, steroids, flavonoids, glycosides, carbohydrates, alkaloids. Their study shows that extracts of leaves of *Pongamia pinnata* Linn. could be used for the management of enteric infection.

Prakash et al. (2009) evaluated the antibacterial influence of methanolic extract of roots of *Caesalpinia pulcherrima* which belong to Fabaceae family. The antimicrobial activity was evaluated using agar cup plate techniques against methicillin-resistant *Staphylococcus aureus* multi drug resistant *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*. The result obtained showed

**Table 22.3** Different phytochemical extracts with isoflavones from *Fabaceae* family with potential cardiovascular treatment properties

| Leaf extract | | | |
|---|---|---|---|
| Plant | Phytochemicals | Cardiovascular treatment | References |
| *Schotia brachypetala* | Phenols and flavonoids | Antioxidant property | Sobeh et al. (2016) |
| *Trifolium pratense*, *Trifolium repens* and *Genistella sagittalis* | Heterosides – daidzin, genistin and ononin. Glycosilated precursors – daidzein, genistein and formononetin | Diminish symptoms of menopause such as cardiovascular disorders and osteoporosis | Hanganu et al. (2010) |
| *T. pannanicum* and *T. pratense* | Phytocompounds of isoflavones | Estrogenic, antioxidative, antiangiogenic and anticancer activities | Kolodziejczyk-Czepas (2012) |
| *T. palladium* and *T. scabrum* | Different isoflavone compounds | Antiplatelet activities | Kolodziejczyk-Czepas et al. (2013) |
| *T. pratense* | Isoflavone malonyl glucosides | Prevents cardiovascular diseases | Toebes et al. (2005) |
| *Lotus subbiflorus*, *Lotus conimbricensis* and *Biserrula pelecinus* | *O*-methylated isoflavone named biochanin A | Neuroprotective, nephroprotective and cardioprotective activities | Barreira et al. (2017) |
| *Glycine max* | Phytoestrogenic isoflavones | Menopause-related cardiovascular complications | Lu et al. (2018) |
| *Glycine max* | Isoflavone-containing protein | Improves vascular function, cholesterol efflux and blood markers | Richter et al. (2017) |
| *Lotus conimbricensis* | Isoflavones | Age related cardiovascular disease | Visnevschi-Necrasov et al. (2016) |
| *Lotus polyphyllos* | Lupinalbins, genistin, sativan and vestitol | Prevent cardiovascular complications | Osman et al. (2015) |
| *L. japonica* | Genome to produce isoflavones | Prevent cardiovascular illness | Takos and Rook (2014) |
| **Root extract** | | | |
| *Eriosema kraussianum* | Pyrano-isoflavone | Prevent hyperglycemia related cardiovascular complications | Ojewole et al. (2006) |
| *Millettia griffoniana* | Griffonianone C | Menopause and estrogen related cardiovascular diseases | Ketcha Wanda et al. (2010) |
| *Radix astragali* | *O*-methylated isoflavone named calycosin | Prevention and treatment of cardiovascular disease | Gao et al. (2014) |

(continued)

**Table 22.3** (continued)

| Leaf extract | | | |
|---|---|---|---|
| Plant | Phytochemicals | Cardiovascular treatment | References |
| *Pueraria lobata* | Isoflavones | Anti-inflammatory and antioxidant activities | Jin et al. (2012) |
| *Trifolium pratense*, roots of lobe Kudzu vine, *Ononsis spinosa* and *Glycyrrhiza glabra* | Isoflavone compounds | Prevention and treatment of cardiovascular disease | Sazdanić et al. (2019), Luo et al. (2017), Addotey et al. (2018) and Tyagi et al. (2018) |
| **Seed extract** | | | |
| *Securigera securidaca* | Isoflavone compounds | Improves vascular endothelium-dependent relaxation in hypercholesterolemia | Garjani et al. (2009) |
| *Lupinus albus* | Isoflavone-poor protein | Reduce hypercholesterolemic condition and elevate LDL receptor activity | D'Agostina et al. (2004) |
| *G. max* | Metabolic engineering to yield more daidzein isoflavone compound | Cardiovascular drug development | Yu et al. (2003) |
| *G. max* | Soybean cyst nematode influenced seed extracted isoflavone | Treatment of cardiovascular ailments | Carter et al. (2018) |
| *T. Pratenses* | Formononetin | Menopause mediated cardiovascular diseases in women | Budryn et al. (2018) |
| Soy and lotus seeds in rice porridge | Isoflavones | Antioxidant activity | Kim et al. (2019) |
| **Other extracts** | | | |
| Flowers of *Lotus japonicus*, *Nelumbo nucifera* and *Lotus conumbricensis* | Isoflavones | Treatment of cardiovascular diseases | Shimada et al. (2003), Deng et al. (2013) and Visnevschi-Necrasov et al. (2016) |
| *Pueraria thomsonii*, red clove, soy bean and Kudzu | Isoflavone | Prevention and treatment of cardiovascular diseases | Hirayama et al. (2011), Xu et al. (2006), Takahashi et al. (2012) and Delmonte et al. (2006) |
| *Glycyrrhiza glabra*, *Caragana changduensis, Maackia amurensis* and *Millettia ferruginea* | Isoflavone compounds | Prevention and treatment of cardiovascular diseases | Parvaiz et al. (2014), Shin et al. (1999), Sun et al. (2015), Maksimov et al. (1985) and Choudhury et al. (2015) |

that the crude extract containing a concentration of 225 8 g/mL exhibited the highest zone of inhibition of 27 mm against *Klebsilla pneumonia* while concentration containing 75 8 g/mL exhibited the least antibacterial effect on *Staphylococcus epidermidis*. Their study shows that the methanolic root extract of *Caesalpinia pulcherrima* could be used as an antibacterial agent.

Sultana et al. (2010), reported the antimicrobial, cytotoxicity and free radical scavenging potential of methanolic extract of *Glycyrrhiza glabra* which belong to the family of Fabaceae. The result obtained shows that the extract of *Glycyrrhiza glabra* inhibited all the test microorganisms with the exception of *Pseudomonas aeruginosa.* The highest sensitivity was observed on *Staphylococcus aureus with* a zone of inhibition of 22 mm while cytotoxic activity had $LC_{50}$ value of 0.771 μg/ml and free radical scavenging activity had $IC_{50}$ values of 87.152 μg/ml.

Chanda et al. (2010) evaluated the antibacterial effectiveness of fruit rind and the seeds of nutraceutical plants which belongs to Fabaceae family. The antimicrobial assessment was performed using agar well diffusion techniques against four gram-negative and four gram-positive bacteria. The result shows that the crude extract obtained from the Fabaceae family exhibited a higher antibacterial activity on gram-positive bacteria when compared to gram-negative bacteria.

Arabi and Sardari (2010) evaluated the antifungal effect of a medicinal plant that belongs to the family of Fabaceae obtained from South and north of Iran. Some of the medicinal plants that belong to Fabaceae used during this study were *Astragalus stepporum, Taverniera cuneifolia, Dalbergia sissoo, Ammodendron persicum, Lathyrus pratensis, Sophora alopecuroides, Oreophysa microphyalla* respectively. The active component was extracted using the Percolation technique with 80% ethanol. The antifungal effect was performed using broth microdilution against *Aspergillus fumigatus* AF 293, *Candida albicans* ATCC 10231, and *Asperigillus niger* ATCC 16404 respectively. The result revealed that all the plants from Fabaceae utilized during this experiment exhibited an antimicrobial effect against at least one of the tested isolates. The study validates the significant of the Fabaceae plant as a therapeutic agent for the management of pathogenic fungi.

Aung (2011) assessed the antimicrobial effectiveness and the level of the phytochemical component present in *Sesbania grandiflora* L. from the family Fabaceae. The chloroform extract exhibit more antimicrobial activity against all the tested isolates most importantly on *Pseudomonas aeruginosa.* The antimicrobial activity demonstrated by the crude extract from the leaves of *Sesbania grandiflora* might be linked to the presence of various phytochemical constituents like α-amino acid, reducing sugar, phenolic compound, terpenoid/steroid, carbohydrate, tannin, flavonoid, saponin, glycoside, and glycoside.

Chaurasia and Saxena (2012), reported the antibacterial effectiveness of 4 different green beans. The aqueous extract from the various green beans were extracted from *Vicia faba* (broad beans; stem), *Vigna unguiculata* (cowpea; lobia), *Phaseolus vulgaris* (French beans), *Cyamopsis tetragonoloba* (cluster beans; guar) and were evaluated against two human pathogenic bacteria which were *Bacillus subtilis* (gram positive) and *Escherichia coli* (gram negative). The antimicrobial assay was performed using disc diffusion techniques. The effectiveness of the aqueous extract was evaluated with streptomycin serving as a control. The result obtained shows that the aqueous extract obtained from the various beans exhibited antimicrobial activity against all the tested bacteria. The antibacterial was shown to be bacteriostatic. The antibacterial activity on *E. coli* varies from 9 mm to 15 mm while *B. subtilis* varies from 10 to 12 mm.

Küçükboyacı et al. (2012), utilized gas chromatography-mass spectrometry to determine various alkaloids available in the *Genista sandrasica* Hartvig & Strid which belong to Fabaceae family grown in Turkey. The percentages of ten quinolizidine alkaloid detected in the plant include anagyrine (40.49%), *N*acetylcytisine (6.48%), baptifoline (10.76%), and 13-methoxylupanine (13.12%) respectively. The antimicrobial effectiveness of the alkaloid extract of *Genista sandrasica* was carried out against the following microorganisms which include *Pseudomonas aeruginosa*, *Candida krusei*, *Staphylococcus aureus, Escherichia coli*, *Candida albicans,* and *Bacillus subtilis.* The minimum inhibitory concentration exhibited by the crude extract from *Genista sandrasica* against *S. aureus* and *B. subtilis* was 62.5 μg/mL and 31.25 μg/mL respectively.

Hossain et al. (2012), evaluated the biological activity of *Cassia senna* leaves including its antimicrobial effectiveness which belongs to Fabaceae family. The crude extract present in *Cassia senna* leaves was extracted using chloroform, methanolic, n-hexane, ethyl acetate respectively. The crude extract was tested against 8-gram (−) bacteria, three fungi and 5-gram (+) bacteria using disc diffusion method. The result shows that n-hexane and chloroform fractions exhibited some level of antimicrobial effect when compared to the methanol extract without any antimicrobial effect.

Pahune et al. (2013) validated the antimicrobial effect of *Clitoria ternatea* Linn which is a species under a genus Clitoria, family Fabaceae. The main aim of their study was to evaluate the utilization of *Clitoria ternatea* Linn as a natural indicator as a permanent replacement to synthetic indicator. The natural indicator will be utilized in numerous acid-base titration. The result reveals that the equivalence points observed from the flower are comparable to the one by the standard indicators. Moreover, the same result was obtained from the weak base and weak acid titration most especially from the flower extract. Furthermore, the methanolic flower extract exhibits a significant antimicrobial effect against *Staphylococcus aureus*. Their research showed that natural indicator is more effective, simple, accurate and economical and eco-friendly when compared to the synthetic indicator most especially for acid-base titration.

Dzoyem et al. (2014) evaluated the effect of acetone leaf extracts of nine medicinal plant that belongs to the family of Fabaceae that has been under-investigated. The antimicrobial activity was performed using a serial microdilution against three Gram-negative and against three Gram-positive bacteria. Moreover, it was observed that 6 out of the 9 acetone extracts exhibited a significant antimicrobial activity with minimum inhibitory concentration values that varies from MIC 20–80 μg/mL against all the tested bacterial species. Among all the plant extract tested, *Crotalaria capensis* showed the highest activity against *Salmonella typhimurium* followed by *Indigofera cylindrical,* with minimum inhibitory concentration value that ranges from 20 μg/mL to 40 μg/mL respectively. Their study established that the plant species from Fabaceae could be utilized as an antimicrobial agent for effective promotion of health and productivity.

Tomar et al. (2014) validated the antimicrobial effect of the methanolic effect of the crude extract obtained from *Mimosa pudica* L which belong to Fabaceae family. The antimicrobial effect was performed using Minimum inhibitory concentration and agar well diffusion techniques. The crude extract of *Bacillus subtilis* MTCC-441, *Pseudomonas aeruginosa* MTCC-4673, *E. coli* MTCC-443, *Staphylococcus aureus* MTCC- 3160, and *Streptococcus pyogenes* MTCC-1926. It was observed that the crudes extract exhibited a board spectrum of antimicrobial efficacy against all the tested isolates. The zone of inhibition, which varies from 17.25 to 20 mm in diameter from the crude extract obtained from *Mimosa pudica* extracts against all the tested microorganism.

Darsini and Shamshad (2015) evaluated the antibacterial efficacy of organic extract from hexane, ethanol, aqueous and methanol of *Clitoria ternatea,* which belong to Fabaceae family. The antimicrobial efficacy was performed using an agar disc diffusion technique. The crude extract was tested against *Proteus vulgaris, Salmonella typhimurium, Candida albicans, Shigella dysenteriae.* The result obtained show that the methanolic extract exhibited the highest antimicrobial activity in comparison to other extracts from water, ethanol, and hexane respectively. The antimicrobial activity of these extracts might be linked to the presence of steroids, tannins, alkaloids, terpenoids, and flavonoids.

Santanaa et al. (2015), validated the medicinal properties of some plants from Fabaceae and were tested against Candida and fungal pathogens. The plant species tested were *Sclerolobium aureum* (Tul.) Baill, *Enterolobium ellipticum* Benth., and *Vatairea macrocarpa* (Benth.) Ducke. The plants were tested against dermatophytes, Leishmania (Leishmania) amazonensis and yeasts. The result revealed that 50% of the total plant screened among the 26 extracts exhibited minimum inhibition concentration of 0.12 to ≤31.25 g/ml while 50% of the total plant obtained from the 6 extracts showed an inhibitory concentration index which varies from 9.23 to 78.65 g/ml. Their study shows that plant from the Fabaceae family could be used as anti-Candida agent and antifungal.

Besong et al. (2016) wrote a comprehensive review of the medicinal importance of *Dialium guineense* which has been reported to be one of the most important plants in Fabaceae family. The plant has been reported to possess numerous medicinal properties which include anti-hemmorrhoidal, antioxidant, anti-plasmodial, vitamin supplement, anti-vibrio, molluscicidal, analgesic, oral care, anti-hepatotoxic, anti-ulcer, and most especially antimicrobial activity.

Aruna and Saravanaraja (2016), reported the antimicrobial activity of *Fabaceae* plant species available. The effect of the extract obtained from these plant species was tested against some indigenous bacterial species. The plant species from the Fabaceae family used during this study include *Pongamia pinnata, Clitoria ternatia, Abrus precatorus, Cassia auriculata, Crotalaria vergosa, Vigna mungo, Sesbania grandiflora, Mimosa pudica, Cajanas cajan, Acacia* *nilotica* and *Tephrosia purpuria*. The result obtained reveals that they all exhibits antimicrobial activity against all the indigenous bacterial isolates from water, soil and samples. Furthermore, greater antimicrobial activity was observed from all the tested plant extract against *E. coli* when least efficacy was observed on *Streptococci spp.*

Velmurugan and Parvathi (2017), evaluated the antifungal efficacy of *Phyllodium pulchellum* L. Desv which belong to the family of Fabaceae. The active compound in the plant was extracted using chloroform, aqueous and ethanol. The extract was tested against *Rhizhotonia solani, Colletotrichum falcatum, Aspergillus niger, and Pencillium notatum*. The result obtains revealed that the ethanolic extract exhibited the highest microbial activity against all the tested isolates when compared to other extracts. The higher antimicrobial activity might be linked to the presence of the flavonoid (71.33 ± 4.172 mg/g), tannin (30.23 ± 3.025 mg/g) and phenol (88.68 ± 2.081 mg/g) respectively. Their study shows that *Phyllodium pulchellum* could be utilized as an antifungal agent for the fungal pathogens.

In Pakistan, Khan et al. (2018), demonstrated that *Cichorium intybus* ethanolic extracts (18 μl/disc) inhibited the growth of *K. pneumoniae* (a gram-negative bacterium) and made the 22.5 ± 0.5 mm zone of inhibition followed by 22 ± 0.1 mm zone of inhibition against the gram-positive bacterium, *B. subtilis* and 19 ± 0.1 mm zone of inhibition against the fungus, *C. albican*. Similarly, the methanolic extract of *Medicago sativa* was found to inhibit *B. subtilis* (gram-positive bacterium), *E. coli* (Gram negative bacterium) and the fungus, *C. albican*.

Heydari et al. (2019), evaluated the antimicrobial and anti-inflammatory activities of methanol extracts and n-hexane, ethyl acetate, chloroform, and water fractions of five Lathyrus species, *namely Lathyrus armenus, Lathyrus aureus, Lathyrus cilicicus, Lathyrus laxiflorus subsp. laxiflorus*, and *Lathyrus pratensis*, growing in Turkey. The results showed that ethyl acetate fractions of the tested species exhibited higher antimicrobial activity than the other extracts. Among all of the tested extracts and fractions, the highest anti-inflammatory activity was detected in water fractions. Furthermore, water fractions of *L. pratensis* showed better anti-inflammatory activity than acetylsalicylic acid and diclofenac sodium, which were used as standard drugs in this assay.

### *22.4.9 Anti-parasitic Activities*

Abdalla and Koko (2018), wrote a comprehensive review based on 53 studies carried out during the period of 1986–2016. The review work was based on the anti-parasitic activity of medicinal plants native to Sudan sourced from previous research work documented from short communications, research papers, MSc and Ph.D. theses, published books, review papers. This data was collated from Science Direct, the Pubmed science web of Knowledge, Google. The result of the search and study shows that 49 plant species belonging to 29 families were screened and evaluated for their anti-parasitic effects during this period. The result obtained shows that family Fabaceae was the most screened which consists of 10 species and exhibited an inhibitory effect against *Plasmodium falciparum*.

## 22.5 Isoflavones: Extraction Procedure

Extraction of isoflavones can be performed using methanol, ethanol, acetonitrile, acetone or their mixtures with water as extraction solvents. Isoflavonoids are present in plant material in free forms, called aglycones, but they are present mostly as glycosides. Due to the relative instability of the glycosides, the extraction method must be carefully considered in order to preserve the original isoflavone profile. Several studies have shown that isolation at high temperatures causes changes in isoflavone composition due to glycoside decomposition (Rostagno et al. 2009). Decarboxylation of malonylglucosides to acetyl glucosides and ester hydrolysis of malonyl and acetyl glucosides to underivatized glucosides are the two most common conversions of glycosides occurring during the extraction process. It is also possible for any conjugated isoflavone to generate the aglycone form by cleavage of the glucosidic bond. Some glycosides, including malonyl and acetyl isoflavones, are particularly unstable (Rostagno et al. 2009). Due to these potential chemical alterations, the use of drastic temperature and pressure conditions and long extraction times may cause degradation of isoflavonoids conjugates, changing the isoflavone profile of the samples and limiting the information obtained. In addition, chemical hydrolysis leads to a marked increase in the concentration of aglycones present in the sample at the expense of the glucosides and hence increase in the available amount of aglycones to be extracted. So, mild extraction techniques like maceration or negative pressure cavitation extraction are often favoured in order to extract the conjugated forms of isoflavonoids intact. For extraction of aglycones, however, more drastic methods, such as microwave-assisted extraction or accelerated solvent extraction, may be performed.

The principles of Green Chemistry, formulated in 1998 by Anastas and Warner, involve friendly products and processes (Gałuszka et al. 2013; Perez and Escandar 2016). The most important areas of GAC associated with the extraction of plant isoflavones are: automation and simplification of the process; increasing operator safety; reduction of sample size, solvent volume and waste production; elimination of toxic reagents and minimization of energy and time.

## 22.6 Distribution of Isoflavone in Different Plants Parts

### *22.6.1 Leaf Extracts*

Isoflavones are widely extracted from the leaves of Fabaceae plants as they are easy to extract and are present in large quantities (Ameer et al. 2017). *Schotia brachypetala* is a South African endemic tree that belongs to the *Fabaceae* family, where the isoflavones are extracted from their leaves using hydro-alcohol as solvents. The result revealed that the isoflavones are present in high quantity. Other phytochemicals that are present in the extracts are flavonoid glycosides, dihydrochalcones, galloylated flavonoid glycosides, anthocyanins, procyanidins, hydroxy benzoic acid derivatives, methyl traces, hydrolysable tannins and acetylated flavonoid derivatives. The synergistic effect of all these phytochemicals in the extracts exhibited enhanced antioxidant activity, both *in vitro* and *in vivo* models which will be beneficial in reducing and preventing cardiovascular diseases (Sobeh et al. 2016). Similarly, the liquid chromatography-mass spectroscopy (LC-MS) analysis of isoflavones that are extracted from the dried blooming aerial parts (herbal leaves) of six different Fabaceae family plants. The result revealed that the combination of isoflavone compound is different in each plant, where *Trifolium pratense*, *Trifolium repens* and *Genistella sagittalis* contains a high concentration of heterosides such as diadzin, genistin, ononin and glycosylated precursors such as daidzein, formononetin and genistein. The study also reported that the presence of different isoflavone combinations in leaves of Fabaceae family makes them a better candidate for extracting isoflavones with positive cardiovascular effects. Further, it was also reported that the leaf extract of *T. pannanicum* ad *T. pratense* contains large quantity and different type of isoflavones that possess enhanced estrogenic, antioxidative, antiangiogenic and anticancer activities which are beneficial in reducing menopausal complaints and preventing cardiovascular diseases (Kolodziejczyk-Czepas 2012). Also, it is noteworthy that the leaf extract of *T. palladium* and *T. scabrum* also possess a unique combination of isoflavones that lead to their enhanced antiplatelet activities to prevent cardiovascular diseases (Kolodziejczyk-Czepas et al. 2013).

Moreover, isoflavone malonyl glucosides are extracted from the leaves of *T. pratense* (red clover) (Toebes et al. 2005) and these isoflavone type are reported to be useful in preventing cancer, cardiovascular diseases and gynaecological problems (Watanabe et al. 2002). The leaves of nine Fabaceae plants such as *Biserrula pelecinus*, *Lotus conimbricensis*, *Lotus subbiflorus*, *Ornithopus compressus*, *Ornithopus pinnatus*, *Ornithopus sativus*, *Scorpiurus muricatus*, *Scorpiurus vermiculata* and *Scorpiurus vermiculatus* were used to extract isoflavones. The result revealed that the isoflavone profiles of each plant are different and the high content of *O*-methylated isoflavone named biochanin A in *lotus* species and *B. pelecinus* will help in the neuroprotective, nephroprotective and cardioprotective activities of these plants (Barreira et al. 2017). In addition, phytoestrogenic isoflavones extracted from the leaves of *Glycine max* (soy beans) help to elevate the calcium and chloride level in premenopausal women, which will eventually reduce the menopause-related cardiovascular complications (Lu et al. 2018). Moreover, it has been reported that the isoflavone-containing protein extracted from the leaves of *G. max* proves to be significant in improving the vascular function, cholesterol efflux and blood markers, along with a slight increase in blood pressure, among adult patients with cardiovascular disease risks (Richter et al. 2017). Furthermore, isoflavones were also extracted from the leaves of lotus species such as *Lotus conimbricensis* which acts as a cure for age related cardiovascular disease (Visnevschi-Necrasov et al. 2016), *L. polyphyllos* to extract lupinalbins and genistin type of isoflavones to prevent cardiac diseases (Osman et al. 2015) and the genome present in *L. japonicus* uplift the production of isoflavones in leaves and exhibited unique mechanism to prevent cardiovascular illness (Takos and Rook 2014). It is noteworthy from all these reports that the leaves of *T. pratense* (red clove) and *Glycine max* (soy bean) are widely used to extract isoflavones, which exhibits improved cardiovascular effects depending on their available combination and quantities.

### *22.6.2 Root Extracts*

Similar to leaves, phytochemical extracts of roots from plants that belong to Fabaceae family contains large quantities of isoflavones and are beneficial in the treatment of cardiovascular diseases. The root extracts of *Eriosema kraussianum* have been reported to possess two significant pyrano-isoflavone. These unique isoflavones are injected into hyperglycemic rat, which reduced their glycemic condition depending on the dose. Further, high concentration of these phytocompounds leads to biphasic effects towards portal veins of rats and long-lasting relaxation of venous muscle strips. This study proved that the root extract of pyrano-isoflavone helps in reducing and preventing hyperglycemia related cardiovascular complications (Ojewole et al. 2006). Likewise, the root extracts of *Millettia griffoniana* yielded a unique isoflavone named griffonianone C and are proved to alter the expression of various genes that are responsive to estrogen in the vena cava of ovariectomized rats. These isoflavones can be useful in preventing women with menopause-mediated cardiovascular diseases (Wanda et al. 2010). Moreover, the root extracts of *Radix astragali* are reported to contain calycosin, which is an *O*-methylated isoflavone, as a major bioactive chemical. These isoflavones are widely useful in the treatment of inflammation, cancer, stroke and cardiovascular diseases (Gao et al. 2014). In addition, the root extracts of *Pueraria lobata* contain large quantities of isoflavones, which exhibited improved anti-inflammatory and antioxidant activities which will be beneficial in reducing cardiovascular complications (Jin et al. 2012). In recent times, the root extracts of *Trifolium pratense*

(Sazdanić et al. 2019), roots of lobe Kudzu vine (Luo et al. 2017), *Ononsis spinosa* (Addotey et al. 2018) and *Glycyrrhiza glabra* have been studied. All these plant root extracts contain different quantities and combinations, depending on the place of growth, nutrient availability and several other factors. However, the isoflavones present in all these root extracts are proven to be useful for the treatment and prevention of cardiovascular diseases.

### 22.6.3 Seed Extracts

The seed extracts of plants from the Fabaceae family were also reported to possess isoflavones with cardiovascular effects. It is noteworthy that the hydroalcoholic seed extracts of *Securigera securidaca* possess a high concentration of isoflavone which possess enhanced vascular reactivity, decrease lipid levels, peroxidation, atherosclerotic lesion and improves vascular endothelial-dependent relaxation in hypercholesterolemia (Garjani et al. 2009). Similarly, the proteins extracted from the seeds of *Lupinus albus* are proved to be natural isoflavone-poor legume. However, these protein extracts are proven to reduce hypercholesterolemic condition and elevate low density lipoprotein (LDL) receptor activity in human hepatoma cell lines (HepG2) which will be beneficial in reducing the hyper-cholesterol related cardiovascular illness (D'Agostina et al. 2004). Further, the isoflavone levels in the seed of *G. max* has been increased via metabolic engineering of phenylpropanoid pathway genes and expressing maize C1 and R transcription factors. These modifications lead to decreased genistein and increase the daidzein levels in the overall isoflavone level. These molecular engineering methods were useful in the accumulation of isoflavone in the seeds of soy bean which will yield more isoflavones to formulate drugs for cardiovascular diseases (Yu et al. 2003). In recent times, it has been revealed that the presence of isoflavone in seed extracts of *G. max* is influenced by genotype and environment as well as the infestation of seeds by nematodes. The direct relationship between soybean cyst nematode and seed isoflavone concentration are emphasized to be useful in elevating the stability of isoflavones, which will be beneficial in yielding better quality isoflavones for the treatment of serious cardiovascular ailments (Carter et al. 2018). Further, the estrogenic activity of *T. pratense* seed extract was evaluated recently and the result revealed that the concentration of isoflavones, especially formononetin, plays a major role in their estrogenic activity which reduces menopause related cardiovascular diseases in women (Budryn et al. 2018). Moreover, the addition of soy and lotus seeds with isoflavones in the rice porridge increases its nutritional value and increases the antioxidant activity which can be taken as a food to strengthen the heart valves and improve cardiac functions among cardiovascular patients (Kim et al. 2019).

### 22.6.4 Other Plant Parts Extracts

Apart from leaves, roots and seeds, the phytochemical extracts from other parts of Fabaceae plants contain isoflavones. The flowers of *Lotus japonicus* (Shimada et al. 2003), *Nelumbo nucifera* (Deng et al. 2013) and *Lotus conumbricensis* (Visnevschi-Necrasov et al. 2016) contains different compounds of isoflavones. Likewise, the flowers of *Pueraria thomsonii* (Hirayama et al. 2011), red clover (Xu et al. 2006), soybean (Takahashi et al. 2012) and Kudzu (Delmonte et al. 2006) were also proved to contain high concentration of isoflavones. In addition, the plant parts of *Glycyrrhiza glabra* (Parvaiz et al. 2014), rhizomes of *Belamcanda chinensis* (Shin et al. 1999), plant parts of *Caragana changduensis* (Sun et al. 2015), heartwood of *Maackia amurensis* (Maksimov et al. 1985) and *Millettia ferruginea* (Choudhury et al. 2015) were also being proved to contain isoflavones in their extracts. These isoflavones will also be useful as a nutritional additives or pharmaceutical agent and curative agent for the treatment of cardiovascular ailments.

## 22.7 Future Scope

It is apparent that the study of isoflavones and their effects on human health will become an ever-increasing topic in the future because of their therapeutic potentials. As our wisdom of specific isoflavones excels, there will undoubtedly be the opening of newer dimensions in newer application forms that will precisely benefit human beings. Research endeavours should be focussed on detailed understanding of different dietary isoflavones so as to harness all the beneficial effects. Studies related to these compounds in an exhaustive and comprehensive way will enhance pharmaceutical exploration in the field of carcinogenic disease prevention. This detailed information will be extremely helpful for the pharmacognosist, ethno botanists, botanist and pharmacologist for the collection and identification of the plant for their research work. Health benefits of isoflavones undoubtedly justify the interest towards a definite direction, but the possible controversial outcomes of some clinical and epidemiological studies reaffirm the need of further investigations and subsequent fine tuning.

## 22.8 Conclusion

Isoflavones are molecules displaying various biological activities with relevance to plant physiology and development. They have an active protective role against harmful abiotic factors and their interactions with other plants and microorganisms. To assess the clinical effects of select foods with a plethora of bioactive compounds containing isoflavones as epidemiologic and cell line evidence, new vistas of health-related research is gaining momentum. Isoflavones are also among the potent dietary factors that offer necessary protection against cancer, heart disease and osteoporosis. Much research is waiting to clearly define the pharmacological effect of dietary isoflavones. In the context of the present as well as forthcoming researches, the role of analytical methods applied for assessment of isoflavones appears to be very crucial.

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