A REVIEW OF FLAVONOIDS AND OTHER PHENOLIC SUBSTANCES FROM MEDICINAL PLANTS FOR PHARMACOLOGICAL AND THERAPEUTIC USES

Ravindra Dnyandeo Mapari
Research Scholar
Department of Pharmacy
Sunrise University, Alwar, Rajasthan.
ravindramapari85@gmail.com

Dr. Tejas Shivram pachpute
Research Guide
Department of Pharmacy
Sunrise University, Alwar, Rajasthan.

Abstract
Antioxidants and bioactive molecules called flavonoids and phenolic compounds have been explored for their potential to treat and prevent a wide range of ailments. In this work, interesting alternative sources for pharmacological and therapeutic uses are reviewed, including flavonoids and other phenolic compounds. The potential use of these phytochemicals from medicinal plants, particularly for health promotion, in pharmaceutical and medical fields are also discussed. They have anti-inflammatory, antioxidant, anti-cancer, cardioprotective, immune-system-boosting, and UV protection properties.
Keywords: *flavonoid; medicinal and pharmaceutical applications; medicinal plants; phenolics*

Introduction
Plant secondary metabolites like flavonoids and other phenolic compounds contain an aromatic ring with at least one hydroxyl group. Plants are the source of more than 8000 phenolic chemicals. Flavonoids, including their methylated derivatives, glycosides, and aglycones, make about half of these phenolic chemicals. Phytochemicals may be found in foods and plants. Effective antioxidants, anticancer, antibacterial, cardioprotective, anti-inflammatory, immune system-promoting, UV radiation protection, and pharmaceutical and medical candidates include flavonoids and other phenolic compounds. Due to their potential health advantages, research on medicinal plant flavonoids and other phenolic compounds has risen recently. Most recent reviews focused on the health effects of phenolics or flavonoids.

This paper reviews current studies on flavonoids and other phenolic phytochems as possible sources of pharmacological and therapeutic advantages and recommends interesting areas for further research. In June 2018, flavonoids, phenolics, and medicinal plants were looked for on Scopus, Google Scholar, and PubMed. The most current and non-redundant papers that achieved the goal of this research were located and examined among the 351 returned articles. To emphasize important ideas, some older articles were picked. 105 carefully chosen journals were used in the study.

Effects of Plant Flavonoids and Other Phenolics on Human Health Promoting, Diseases Curingand Preventing

Antioxidant Effects
ROS and RNS are created when cells consume oxygen to create adenosine triphosphate (ATP). When ROS and RNS are in balance, they improve cellular health and immune responses, but when

they are out of balance, they lead to oxidative stress and chronic and degenerative diseases. More research is being done on the utilization of natural antioxidants. Synthetic antioxidants, which are thought to cause cancer, are being replaced with natural antioxidant molecules. For instance, medicinal plants may include naturally occurring antioxidant molecules derived from secondary metabolites like flavonoids and phenolic substances that plants produce to protect themselves or promote development under adverse situations. Functional group organization, structure, substitution, and quantity were all impacted by the antioxidant properties of flavonoids, which also included metal ion chelation and radical scavenging. The primary phytochemical antioxidants found in plants are flavonoids and phenols.

Diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity was used by Oki and his colleagues to study the antioxidant activity of anthocyanins and other phenolic compounds from many types of purple-fleshed sweet potatoes (Ipomoea batatas (L.) Lam.), a significant food and medicine in Japan. Phenolic content and free-radical scavenging activity had a favorable correlation. Chlorogenic acid serves as the primary DPPH radical-scavenger in the "Miyanou-36" and "Bise" cultivars of I. batatas, although anthocyanins were present in the "Ayamurasaki" and "Kyushu-132" cultivars. Mishra and his colleagues investigated the medicinal herb Bauhinia variegata L., which is utilized in Pakistan, India, and other Asian nations. B. variegate leaf extracts included flavonoid components that decreased oxidative damage, bound iron, and neutralized free radicals. From six Spanish Mediterranean Opuntia ficus-indica (L.) Mill cultivars, Andreu and colleagues assessed the antioxidant activity and phytochemical characterisation of juvenile and mature cladodes, fruit peel, and fruit pulp. Due to its high phenolic content, the best antioxidant cultivar decreased oxidative stress. Aesculus indica (Wall. ex Cambess.) Hook is a medicinal plant from temperate Asia, including Pakistan, Nepal, India, and Afghanistan. Zahoor researchers investigated the antioxidant and bioactive components in the fruits of this plant. We discovered similarities between mandelic acid and 2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxy-4H-Chromen-4-one (quercetin). Due to its phenolic composition, the Indian medicinal plant Polygonatum verticillatum (L.) All. has antioxidant activity in rhizome extracts. Meng's team looked at the wild tea plant Camellia fangchengensis S. Ye Liang and Y.C. Zhong, which is utilized by villagers in the Republic of China's Guangxi region to create green or black tea. This species possesses a lot of flavan-3-ol oligomers and monomers, which are antioxidants.

Gymnosperms, or plants with necked seeds, also contain antioxidant phenolic compounds in addition to angiosperms. Utilizing twig and needle extracts, researchers looked at the phytochemical components and antioxidant properties of five Turkish Pinus species, including P. brutia Tenore's Turkishpine, P. pinea L.'s stone pine or umbrella pine, P. halepensis Miller's Aleppo pine, P. sylvestris L.'s Scots pine, and P. nigra J.F. Arnold's European black pine. The highest total phenol concentration and antioxidant activity were found in pycnogenol. Pinus cembra L., a native of the Central European Alps and Carpathian Mountains, was the subject of research by Apetrei and colleagues. Compared to needle extract, the hydromethanolic extract of bark included higher total phenolics and flavonoids. Better free radical scavengers include bark extract.

Antibacterial Effect

It's interesting to note that phenolic and flavonoid antibacterial chemicals are present in both blooming and non-flowering medicinal plants. Gliricidin 7-O-hexoside and quercetin 7-O-rutinoside are compounds found in Asplenium nidus nidus L. that may be effective against Proteus mirabilis, vulgaris, and aeruginosa (Schroeter) Migula. Flavonoid and phenolic chemicals are produced by several culinary and medicinal plants. In Indonesia and other South East Asian countries, nutmeg (Myristica fragrans Houtt.) is used as a flavoring. Including Providencia stuartii Ewing and Escherichia coli (Migula) Castellani and Chalmers, MDR gram-negative bacteria are eliminated by the ethanolic extract of nutmeg seeds, which contains 3′,4′,7-trihydroxyflavone. Pseudarthria hookeri Wight and Arn is a medication used to treat cough, diarrhea, stomachaches, and pneumonia in Africa. The flavonoids from this medicinal species, including E. coli, Klebsiella pneumonia (Schroeter) Trevisan, Pseudomonas aeruginosa (Schroeter) Migula, and Enterococcus faecalis (Andrew and Hor), were discovered by Dzoyem and his team to be the most effective against both gram-positive and gram-negative bacteria. Additionally, Rajarathinam and his colleagues discovered that an extract from the aerial portion of Trianthema decandra L. demonstrated antibacterial action against Pseudomonas aeruginosa (Schroeter) Migula, a resistant strain that was the source of several medical problems. This compound is 2-(3′,4′ dihydroxy-phenyl) 3,5,7-trihydroxy-chromen-4-one. Flavonoids and other phenolic compounds are not effective against P. acnes, the primary cause of acne. In order to lessen P. acnes, kaempferol, which is produced from Impatiens balsamina L., worked more synergistically with clindamycin and quercetin. Studies using flavones from the root of Scutellaria baicalensis Georgi shown their antibacterial activity against skin inflammation caused by P. acnes in both in vitro and in vivo settings. The primary phenolic ingredient identified in Pu'er tea leaves, Camellia sinensis var. assamica (J.W. Mast.), was strictinin. This was looked into by Hsieh's team. Strictinin was successful in combating this bacteria. Phenols in the kernel extract of Mangifera indica L. prevent P. acnes from growing.

Anti-Cancer Effect

One of the biggest causes of mortality worldwide is cancer, which may be brought on by too many or too few free radicals like ROS and RNS. Chemotherapy is a common cancer treatment, although it has a number of disadvantages. Chemotherapy could not be beneficial. Therefore, affordable cancer therapies without side effects are desirable. The plant Dysoxylum binectariferum (Roxb.) Hook.f. ex Bedd. is used to make the drug flavopiridol. [At the time of writing, the actual scientific name for the treatment for lymphoma and leukemia is Dysoxylum gotadhora (Buch.-Ham.) Mabb. Numerous cancers are also prevented and treated using nutritional supplements. It is recognized that phenolic chemicals, particularly flavonoids, help prevent cancer.

The two principal Zingiberaceae species, Zingiber officinale Roscoe and Curcuma longa L., were the subjects of an investigation by Danciu and colleagues on the phenolic composition and biological effects of ethanolic extracts from the rhizomes. As a result of its possible anticancer effects on the B164A5 murine melanoma cell line, this study suggested employing C. longa rhizome extract to treat malignant melanoma. The antitumor activity of polyphenol compounds may potentially be enhanced. According to many biomedical research teams, flavonoids may cause certain cancer cells to undergo apoptosis. A flavonol called quercetin may prevent breast and prostate cancer. For HepG2 and HeLa cells, the flavonoids gliricidin 7-O-hexoside and quercetin 7-O-rutinoside from the medicine fern (Asplenium nidus) were also thought to have chemopreventive properties. Quercetin's capacity to initiate apoptosis has been investigated by Hashemzaei and his associates both in vitro and in vivo. They examined the anticancer properties of quercetin in nine cancer cell lines in vitro: human prostate PC3 cells, colon carcinoma CT-26 cells, pheocromocytoma PC12 cells, acute lymphoblastic leukemia (ALL) cells, prostate adenocarcinoma LNCaP cells, ovarian cancer MOLT-4 T-cells, estrogen receptor-positive breast cancer CHO, and human myeloma U266B cells. Quercetin significantly decreased tumor volume and growth in in vivo animal models of the MCF-7 and CT-26 malignancies (p 0.001). Animals given quercetin tests survived longer. The ASANPaCa, AsPC1, and PANC1 primary pancreatic cancer cell lines were used in the Clifford research team's examination of the anticancer properties of quercetin in patient-derived pancreatic tissue. The signaling receptors created by the well-known gene notch are essential for healthy development, cell fate determination, cell proliferation, and cell survival. Oncogenes and symmetric cell division are also marked by it. Quercetin may have an impact on how pancreatic cancer self-renews, according to Clifford's team. In their examination of the molecular effects of genistein on prostate cancer, Adjakly and his associates demonstrated how this soy isoflavone reduced the nuclear factor kappa B (NF-B) signaling pathway, which regulates cell survival and demise. Additionally, prostate cancer cell growth, mortality, metastasis, and epigenetic changes may be inhibited by soy isoflavone. A phenolic compound called curcumin prevents skin cancer. Phenolics that promote apoptosis may affect the cell cycle. Curcumin's antiproliferative properties on B16F10 murine melanoma cells were investigated in vitro by Abusnina and colleagues. Curcumin inhibited the development of melanoma cells by activating the epigenetic integrator UHRF1. Dietary curcumin may stop this cancer and alter gene expression via epigenetic regulation. It's interesting that the Hisamitsu group used in vitro and in vivo models to limit intracrine androgen production as a way to investigate curcumin's ability to cure prostate cancer. Curcumin inhibited the expression of genes encoding steroidogenic acute regulatory proteins in vitro using human prostate cancer cell lines, including LNCaP and 22Rv1 cells, hence lowering testosterone production. In this experiment, curcumin decreased cell proliferation and death in a dose-dependent manner. Curcumin oral administration for one month controlled the expression of steroidogenic enzymes, including AKR1C2, and inhibited prostate cancer cell growth by lowering testosterone levels in TRAMP mice's prostate tissues in an in vivo study using the transgenic adenocarcinoma of the mouse prostate (TRAMP) model.

Cardioprotective Effects

Plant phenolic and flavonoid chemicals with cardioprotective properties have been investigated for a long time. Doxorubicin, a drug used to treat breast, leukemia, and lymphoma tumors, may cause cardiac problems such myocarditis, pericarditis, arrhythmias, and abrupt heart failure. According to Razavi-Azarkhiavi's study, phenolic substances protect against the cardiotoxicity of doxorubicin. In vitro, in vivo, and clinical studies have shown that antioxidant phenolics reduce the side effects of this anticancer medicine by limiting ROS production, mitochondrial dysfunction, apoptosis, NF-kB, p53, and DNA damage. The Razavi-Azarkhiavi team found that kaempferol, rutin, luteolin, and resveratrol protected against doxorubicin-induced cardiotoxicity without affecting the drug's anticancer effectiveness. Isorhamnetin held my interest. It decreased cardiotoxicity and improved the antitumor efficiency of doxorubicin. The phenolic content of Polish medicinal herbs Centaurea daghestanica (Lipsky) Wagenitz and Centaurea borysthenica Gruner aerial methanolic preparations was examined. Cardiomyocytes treated with doxorubicin were shielded by these two plants. Oxidative stress, cell viability, and mitochondrial membrane potential were all preserved in doxorubicin-exposed rat cardiomyocytes by C. borysthenica and C. daghestanica extracts. The fact that doxorubicin efficacy was unaffected by C. daghestanica methanolic extracts attracted our study. The cardioprotective abilities of Phoenix dactylifera L. were examined by Alhaider's team. The total flavonoid, total phenolic, in vitro antioxidant, and in vivo rodent myocardial infarction of fruit extracts from four eastern Saudi Arabian date palm cultivars were examined. Fruit extracts recruited bone marrow progenitor cells to repair ischemic tissue in vivo myocardial infarction models because of their high phenolic and flavonoid content. In H9c2 cardiac cell lines exposed to tertiary butyl hydrogen peroxide-induced oxidative stress, LDL oxidation, HMG-CoA reductase, and angiotensin-converting enzyme modulation, Syama and colleagues investigated the major phenolic acids and flavonoids from Syzygium cumini (L.) Skeels seeds extract fractions and their cardioprotective potential. The phytochemicals gellagic, syringic, gallic, ferulic, cinnamic, and quercetin were abundant in the fractions. In H9c2 cardiomyoblasts, these fractions decreased oxidative stress, and molecular docking showed a positive correlation between the principal phytochemical compounds and cardiovascular disease-preventing enzymes like angiotensin converting enzyme. The Garjani team examined the cardioprotective effects of an aerial parts extract from the Iranian medicinal plant Marrubium vulgare L. in an in vivo Wistar rat model. The total phenolic and flavonoid content of the extract's aqueous fraction was evaluated using the Langendroff method, as well as its impact on rat cardiac ischemia-reperfusion injury. Cardioprotective effects of M. vulgare extract in water. Phenylpyruvic acid-2-O-D-glucoside and R. Dahlgren's aspalathin may help avoid myocardial infarction brought on by persistent hyperglycemia. Another isoflavone called puerarin works by opening the Ca2+-activated K+ channel and triggering protein kinase C to shield the heart from ischemia and reperfusion. Sprague-Dawley rats were used in vivo. In an in vivo rat model with cardiovascular risk factors, Tian and colleagues examined the potential cardioprotective effects of apple peel and apple flesh polyphenolic extracts. Apple skins protected the heart. Polyphenolic extracts from apple peel may include more phenolics and flavonoids.

Skin Protective Effect from UV Radiation

UV rays cause skin damage. Skin is destroyed by high ROS production. There are several solutions for skin protection. Flavonoids and phenols have the potential to act as UV-protective phytochemicals. Flavonoids function as antioxidants and photoprotectants by chelating iron with the lipids and proteins of cell membranes. They affect a number of signaling pathways and inhibit xanthine oxidase, which produces ROS and oxidative stress. Phenolic antioxidants may help treat skin conditions brought on by UV radiation.

Skin is protected from UV rays by apigenin. Quercetin may be found in Hypericum perforatum L. leaves, apple peel, and onion skin. Hairless mice were shielded from UVB damage by topical quercetin. In UVB-irradiated rats, a ginkgo biloba L. extract with a high quercetin derivative concentration reduced the symptoms of sunburn, suggesting that oral consumption may help prevent and cure sunburn. Silybin, a substantial active component, is present in silymarin, a standardized extract of milk thistle flavonolignans. Human epidermal keratinocytes and fibroblasts were protected against apoptosis in vitro by silymarin topical treatment via improving UVB-induced DNA repair. The soy isoflavone genistein prevents UV-induced DNA damage and photocarcinogenesis in an in vitro skin model. During UVB-induced senescence, Wang and colleagues also discovered that genistein preserved antioxidant enzyme activity and reduced mitochondrial oxidative stress in human dermal fibroblasts. Equol is a metabolite of the isoflavonoid daidzein, also known as genistein. Equol shields DNA from photodamage and guards against immunosuppression, UV-induced erythema-associated edema, and skin cancer in hairless mice. Additionally, Choi and his coworkers found that topical administration of extracts from used coffee grounds, which include flavonoids and caffeine, protected the skin of hairless mice against UVB-induced photoaging by preventing matrix metalloproteinases. For 28 days, the Kano research group observed how oral isoflavones from fermented soymilk products affected the photodamage in ovariectomized hairless individuals. The results show that mice's blood and skin have higher concentrations of isoflavones, which rapidly scavenge reactive oxygen species created by UV radiation and function estrogenically to protect the skin of the animal model.

Naturally Occurring Plant Phenolics and Flavonoids for Menopausal and Post-Menopausal Women

Both manmade chemical compounds and phytochemical substances have advantages and disadvantages in the fields of pharmacy and medicine. In the large-scale drug development process, synthetic chemicals or medications may be produced fast and easily, and they can be modified for patient use in a variety of ways. Contrarily, many artificial (or synthetic) chemical substances, especially long-term therapies, have a number of negative side effects. Because of their negative side effects, certain synthetic medications were rejected for use in clinical therapies. Synthetic estrogen is a prime example, since it was once widely utilized in hormone replacement treatment for menopausal women. Long before several studies showed its unfavorable side effects, such as an increase in the risk of breast, uterine, and ovarian malignancies, these synthetic chemical compounds might effectively alleviate menopausal symptoms.

Estrogen is a sex hormone that primarily regulates women's menstrual cycles and reproductive processes. Due to the ovary's inability to respond to the pituitary, estrogen levels in postmenopausal women are reduced. Cardiovascular illness is one of the numerous postmenopausal symptoms that are brought on by a drop in estrogen levels. The risk of cardiovascular disease will particularly rise in postmenopausal women who also have metabolic syndrome (MetS). In postmenopausal women with metabolic syndrome, flavonoid supplementation may also enhance cardiovascular function, according to studies by Squadrito and his team. The flavonoid phytoestrogen genistein is a clear example of an intriguing alternative for enhancing endothelial functioning in postmenopausal women with MetS. 120 postmenopausal women with type-2 diabetes and no history of cardiovascular disease participated in Gregorio's study, which examined the effects of genistein supplementation on heart function in postmenopausal women with MetS. By adopting a computer-generated double-blind randomization, the patients were evenly split into 2 groups: the Genistein supplementation group and the control group, which received a placebo. According to the findings, genistein may help postmenopausal women with MetS by improving their cardiac function.

Profiling Works and the Survey of Flavonoids and Other Phenolics from Medicinal Plants

Since over four million years ago, flavonoids and other beneficial plant phenolic chemicals have kept people healthy. Flavonoids and phenolics are examples of plant secondary metabolites. Chemical components depend on the mineral makeup of the soil and the kind of plant. Recent studies on medicinal plants have concentrated on natural phenolic compounds like flavonoids.

Despite extensive research on flavonoids and other phenolic compounds, the distinctive components of many local or indigenous medicinal plants have yet to be identified. These procedures seek for and create phytochemical medications. Numerous medicinal plants may be found in Thailand, China, and Japan. Functional studies on several medicinal plant compounds are lacking. In the more than 100 scientific publications we looked at, we discovered phenolics and flavonoids in the flowers, leaves, stems, roots, and rhizomes of medicinal plants. Comparing harvesting season, cultivar, and plant species variation is done using phytochemical profiling.

Future Perspectives and Interesting Directions for Future Researches

1. Everyone must be able to purchase medications and other medical supplies. As a result, the compounds flavonoid and phenolic, which are present in large amounts in many plants, may be pertinent molecules for developing drugs and medical products.
2. The biological, phenolic, and flavonoid activities of medicinal plants may vary across cultivars. Therefore, several therapeutic plant species should be studied in medical and pharmaceutical research.
3. Locations of the source plant material should be compared in further research. This article has already mentioned how the quality and amount of phytochemical components varies depending on environmental factors such soil nutrients and minerals.
4. Local medicinal plant species and indigenous or wild species are important for next research to find novel phytochemical compounds to enhance the availability of medical and pharmaceutical raw materials.
5. Numerous well-known flavonoid and phenolic compounds' molecular mechanisms and signaling pathways need to be investigated in order to enhance therapeutic development.
6. Verifying plant extract findings using components that have been purified.

Conclusions

In order to improve health and treat different ailments, phenolic compounds and flavonoids may be used as bioactive agents in the pharmaceutical and medical sectors. It takes thorough profiling and surveys of medicinal plants to find and produce these phytochemical substitutes. Prospective chemicals should be examined in vitro, in vivo, and clinically in biomedical and pharmaceutical research to ascertain their safety, effectiveness, and side effects.

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