Review Article

Astragalin: A Bioactive Phytochemical with Potential Therapeutic Activities

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Received 8 January 2018; Revised 5 April 2018; Accepted 12 April 2018; Published 2 May 2018

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Natural products, an infinite treasure of bioactive chemical entities, persist as an inexhaustible resource for discovery of drugs. This review article intends to emphasize on one of the naturally occurring flavonoids, astragalin (kaempferol 3-glucoside), which is a bioactive constituent of various traditional medicinal plants such as *Cuscuta chinensis*. This multifaceted compound is well known for its diversified pharmacological applications such as anti-inflammatory, antioxidant, neuroprotective, cardioprotective, antiobesity, antiosteoporotic, anticancer, antiulcer, and antidiabetic properties. It carries out the aforementioned activities by the regulation and modulation of various molecular targets such as transcription factors (NF-κB, TNF-α, and TGF-β1), enzymes (iNOS, COX-2, PGE2, MMP-1, MIP-1α, COX-2, PGE-2, HK2, AChE, SOD, DRP-1, DDH, PLCγ1, and GPX), kinases (JNK, MAPK, Akt, ERK, SAPK, IκBα, PI3K, and PKCβ2), cell adhesion proteins (E-cadherin, vimentin PAR-2, and NCam), apoptotic and antiapoptotic proteins (Beclin-1, Bcl-2, Bax, Bcl-xL, cytochrome c, LC3A/B, caspase-3, caspase-9, procaspase-8, and IGF), and inflammatory cytokines (SOCS-3, SOCS-5, IL-1β, IL-4, IL-6, IL-8, IL-13, MCP-1, CXCL-1, CXCL-2, and IFN-γ). Although researchers have reported multiple pharmacological applications of astragalin in various diseased conditions, further experimental investigations are still mandatory to fully understand its mechanism of action. It is contemplated that astragalin could be subjected to structural optimization to ameliorate its chemical accessibility, to optimize its absorption profiles, and to synthesize its more effective analogues which will ultimately lead towards potent drug candidates.

1. Introduction

Medicinal plants have been an infinite source of therapeutic agents since millions of years. Most of the discovered drugs either belong to natural products or derivatives of natural compounds [1, 2]. The actual fact is that nature is the creator of seemingly limitless series of molecular structures. These structures can serve as unlimited sources for the development of drugs, robust chemotypes, and pharmacophores which are able to be amplified into scaffolds of novel drugs for the cure of various ailments [3]. Before the advent of the postgenomic era with high throughput screening, approximately 80% of drugs were either pure extracts of medicinal plants or the semisynthetic analogues of various compounds from natural sources [4]. After the second world war, the pharmaceutical research expanded to massive screening of plant extracts in search of new drugs from natural resources [5]. To date, about 61% of anticancer and 49% of anti-infective compounds have been discovered from natural products [6].

The term “natural products” encompasses chemical entities derived from plants, bread molds, microorganisms, terrestrial vertebrates as well as invertebrates, and marine organisms [7]. These chemical entities are known to have immense chemical diversity with outstanding drug-like
properties that contribute towards their multitargeted action [8]. A lot of plant-derived bioactive compounds are used for the cure as well as for the prevention of several diseases. Among these compounds are the polyphenols consisting of alcohols with ≥2 benzene rings and ≥1 hydroxyl group. These polyphenols have a range from simple structural molecules (flavonoids and phenylpropanoids) to highly complex compounds (lignins and melanins). Reports have suggested that polyphenols in general and flavonoids in particular exhibit various biological effects like antiallergic, antibacterial, anti-inflammatory, antiviral, antithrombic, hepatoprotective, antitubercular, and antioxidant activities [9].

Flavonoids are structurally diverse and most abundantly found polyphenols in the human diet [10]. They are mostly found in the form of glycosides and acylglycosides. Flavonoids have been divided into various classes such as flavones, flavonols, flavanones, flavanols or catechins, and anthocyanins. They are the essential constituents of our food and are found in onions, parsley, berries including blue berries, black tea, green tea, bananas, red wine, all citrus fruits, sea blackthorns, and dark chocolates with the contents of 70% or more [11].

Astragalin (kaempferol-3-O-β-D-glucoside), a bioactive natural flavonoid, has been well known for its medicinal importance. It has been reported to exhibit multiple pharmacological properties including antioxidant [12, 13], anti-inflammatory, antiviral, antiulcer, and antifibrotic as shown in Figure 2. Various in vivo and in vitro investigations on astragalin have elucidated its medicinal characteristics and mechanism of actions.

2. Natural Sources of Astragalin

Astragalin, a naturally occurring flavonoid, has been identified in a variety of plants (Figure 1 and Table 1) such as Cuscuta chinensis Lam., a member of the Convolvulaceae family, which consists of about 60 genera and 1,650 species. The seeds of the genus Cuscuta are a rich source of astragalin and are utilized as a traditional folk medicine to cure osteoporosis in various Asian countries including Pakistan [17]. C. chinensis has high contents of astragalin, that is, 29–34% of total phenolics as compared to other species [18]. Cassia alata belongs to the family Fabaceae (the largest family among angiosperms) that comprises of ~700 genera and 20,000 species. The leaves of C. alata are found to be effective against skin diseases including eczema and chronic skin impurities in tropical regions of the world (Malaysia, Brazil, and Indonesia) [19]. Astragalin has also been isolated from the plants of Ebenaceae, Rosaceae, and Eucommiaceae families. The summary of plants containing astragalin, parts utilized, and biological features are enlisted in Table 1.

Astragalin can also be produced in vivo by glycosylation of kaempferol at the 3C-O position [20]. UDP-dependent glycosyltransferases (UGT) were used as biocatalysts in the synthesis of astragalin. A recombinant strain of Arabidopsis thaliana was used to construct an efficient UDP-glucose synthesis pathway by use of enzymes such as uridylyl-transferase, sucrose phosphorylase, and sucrose permease. BL21-II was a recombinant strain designed to scale up the production of astragalin by using a fed-batch fermentator.

3. Biological Activities of Astragalin and Their Mechanisms of Action

The biologically active and therapeutically effective compound “astragalin” has been known to possess broad spectrum of pharmacological features such as anticancer, anti-inflammatory, antioxidant, neuroprotective, antidiabetic, cardioprotective, antiallergic, and antibacterial as shown in Figure 2. Various in vivo and in vitro investigations on astragalin have elucidated its medicinal characteristics and mechanism of actions.

3.1. Anti-inflammatory Activity. Inflammation is an immediate response of a body to tissue damage caused by pathogens and toxic stimuli such as physical or chemical injury. Although inflammatory response is a defense mechanism, but if persistent, it can lead to multiple pathological conditions such as cancer, allergy, atherosclerosis, and autoimmune diseases [119]. Negative after effects associated with nonsteroidal type anti-inflammatory drugs (NSAIDs) arouse a need among researchers to find out effective and safe alternatives [120]. Plant extracts enriched with flavonoids have been known to possess anti-inflammatory activity [121].

Astragalin, a bioactive natural flavonoid, has been known to mitigate inflammation in LPS-induced murine model of mastitis and lung injury model via reducing the activity of myeloperoxidase and the expression of IL-1β, IL-6, and TNF-α. Astragalin’s anti-inflammatory response proceeds via inhibition of LPS-induced activation of NF-κB, as it is actively involved in alleviating the deterioration of IkBα and restricting the nuclear translocation of NF-κB.
### Table 1: Plants containing astragalin as an important constituent with its biological properties.

| Name of the plant | Botanical name | Common name | Parts used/extract | Biological activities | References |
|-------------------|----------------|-------------|--------------------|-----------------------|------------|
| **Acer truncatum**| Shantung maple | — | Aerial parts | Antioxidant | [21] |
| **Aceriphyllum rossii**| Mukdenia | — | Aerial parts | Antihemorrhagic, antiplatelet, antioxidant, and acetylcholinesterase inhibitory | [22] |
| **Agrimonia pilosa**| Hairy agrimony | — | Aerial parts | Antimicrobial | [23] |
| **Allium ursinum**| Wild garlic | — | Flowers | Antimicrobial | [24] |
| **Allium victorialis**| Alpine leek | — | Leaves | Antitumor | [25] |
| **Alsophila spinulosa**| Hook tryon | — | Leaves | Antixanthine oxidase | [26] |
| **Apocynum venetum**| Luobuma | — | Leaves | Lower blood pressure, antidepressant, antinephritis, and antineurasthenia | [27] |
| **Jasminum subtriplinerve**| — | — | Aerial parts | Antioxidant | [28] |
| **Astragalus hamosus**| Dwarf yellow milk vetch | — | Aerial parts | Antiulcer, anti-inflammatory, hypoglycemic, and antioxidant | [29] |
| **Caesalpinia decapetala**| Mysore thorn | — | Leaves | — | [30] |
| **Calligonum polygonoides**| Phog | — | Aerial parts | — | [31] |
| **Camellia sinensis**| Tea | — | Leaves and seeds | Antidysentery, antihyperglycemia, and anti-inflammatory | [32–35] |
| **Carthamus lanatus L.**| Downy safflower | — | Aerial parts | Antioxidant | [36] |
| **Cassia alata**| Ringworm bush | — | Leaves | Antioxidant, anti-infectious, and DNA repair | [37] |
| **Celastrus genmannus**| Chinese bittersweet | — | Leaves | — | [38] |
| **Centella asiatica**| Asiatic pennywort | — | Leaves | Anti-inflammatory | [39] |
| **Clerodendrum philippinum**| Chinese glory bower | — | Roots | — | [40] |
| **Coryza filaginoides**| Laennecia filaginoides | — | Aerial parts | Antiproteozal | [41] |
| **Cuscuta chinensis**| Chinese dodder | — | Seeds | Inhibits the histamine | [42] |
| **Cuscuta australis**| Australian dodder | — | Seeds | — | [43] |
| **Dioica teres**| Buttonweed | — | Whole plant | — | [44] |
| **Drosera peltata**| Sundew | — | Aerial parts | Antitussive | [45] |
| **Eucommia ulmoides**| Moroheiya | — | Leaves | Antidiabetic, antioxidant, and hypnotic effect | [46] |
| **Eupatorium cannabinum**| Hemp agrimony | — | Aerial parts | — | [47] |
| **Eupatorium lindleyanum**| Japanese hemp agrimony | — | Aerial parts | — | [48] |
| **Exochorda racemosa**| Pearlbrush | — | — | — | [49] |
| **Flaveria bidentis (L.) Kuntze**| Coastal plain yellow tops | — | Leaves | — | [50] |
| **Flos gossypii**| — | — | Flowers | — | [51] |
| **Gladiolus candidus**| Gladiolus | — | Aerial parts | — | [52] |
| **Glycyrrhiza glabra**| European licorice | — | Leaves | — | [53] |
| **Glycyrrhiza uralensis**| Chinese licorice | — | Leaves | — | [54] |
| **Gynura procumbens**| Longevity spinach | — | Leaves | — | [55] |
| **Hedera helix**| English ivy | — | — | — | [56] |
| **Helianthemum glomeratum**| Island rushrose | — | Aerial parts | — | [57] |
| **Hemistepta lyra**| Whole plant | — | Whole plant | — | [58] |
| **Hippophae rhamnoides**| Sea buckthorn | — | Leaves | — | [59] |
| **Ipomoea batatas**| Sweet potato | — | Leaf | — | [60] |
| **Koelreuteria paniculata**| Golden rain tree | — | Flowers | Antioxidant | [61] |
| **Allium ampeloprasum**| Wild leek | — | Leaves | Antioxidant | [62] |
| **Ligusticum chuanxiong**| — | — | Aerial parts | — | [63] |
| **Lindera aggregata**| Evergreen linda | — | Leaves | — | [64] |
| **Lisetra coreana**| — | — | Leaves | — | [65] |
| **Mangnolia fargesii**| — | — | Flowers | — | [66] |
| **Moringa oleifera**| Drumstick tree | — | Leaves | Antioxidant | [67] |
| **Morus alba L.**| White mulberry | — | Leaves | Hypoglycemic and antioxidant | [68] |
| **Musanga cecropiae**| Forest star | — | Leaves | — | [69] |
| **Nelumbo nucifera**| Sacred lotus | — | Leaves | Lipolytic activity | [70] |
| **Ochradenus baccatus**| Tally weed | — | Aerial parts | — | [71] |
| **Orostachys japonica**| Rock pine | — | — | Calpain inhibitory activity | [72] |
| Name of the plant | Botanical name | Parts used/extract | Biological activities | References |
|-------------------|----------------|-------------------|-----------------------|------------|
| Diospyros kaki    | Japanese persimmon | Leaves | Angiotensin converting enzyme activity, and inhibition of atopic dermatitis (AD) | [12, 87–89] |
| Rosa agrestis      | Field briar | Leaves | Anti-inflammatory and antioxidant | [13, 90–92] |
| Peucedanum alsaticum | — | Fruits | — | [93] |
| Phaseolus vulgaris L. | Common bean | Aerial parts | Antiallergic | [95] |
| Phlomis spinidens  | — | Aerial parts | Antibacterial and anti-inflammatory | [96] |
| Polyanthus muellerianus | — | Leaves | Antifungal | [97] |
| Polygala cyparissias | — | — | DPPH-free radical scavenging activity | [98] |
| Polygonum salicifolium | Knotweed | Aerial parts | Anti-inflammatory | [99] |
| Prunus padus L.    | European bird cherry | Flowers | — | [100] |
| Prunus serotina Ehrh | Black cherry | Flowers | — | [101] |
| Pseudotsuga menziesii | Oregon pine | Needles | Cytoxic | [102–104] |
| Radix astragali    | Milk vetch root | Roots | Antiosteoporotic | [105] |
| Rhus sylvestris    | Sumach | Stems and leaves | Antioxidant | [106] |
| Rosa soulieana     | Shrub rose | Flowers | — | [107] |
| Rubus rigidus var. camerunensis | Ronce blanche | Aerial parts | — | [108] |
| Sapium sebiferum   | Chinese tallow | Leaves | — | [109] |
| Solenostemma argel | Arghel | Aerial parts | Antibacterial | [110] |
| Solidago canadensis L. | Canada goldenrod | — | Antioxidant | [111] |
| Sorbus aria (L.) | Lutescens | Leaves | Antimicrobial and anti-inflammatory | [112] |
| Tadahagi triquetrum | — | Whole plant | Antimicrobial and anti-inflammatory | [113] |
| Tiarella polyphilla | Foam flower | Whole plant | — | [114] |
| Trachelospermum jasminoides | Confederate jasmine | Leaves | — | [115] |
| Urtica cannabina   | — | Fruits | — | [116] |
| Vahlia capensis    | — | — | Antibacterial | [117] |
| Vicia calcarata    | Few flowered vetch | Aerial parts | Hepatoprotective | [118] |
| Wedelia chinensis  | — | Whole plant | Inhibitor of the complement system | [119] |

Figure 2: Biological activities of astragalin.
of free radicals may affect the balance of prooxidant and antioxidative impacts on cellular functions. Excessive production of free radicals in biological systems [75].

Table 2: Anti-inflammatory activities of astragalin in vitro and in vivo.

| Assay                                              | Organism tested                  | Dose/concentration | Molecular targets                                      | References |
|----------------------------------------------------|----------------------------------|--------------------|--------------------------------------------------------|------------|
| LPS-induced mouse mastitis                         | Mouse mastitis                   | 10, 25, and 50 mg/kg | TNF-α↓, IL-1β↓, IL-6↓, p65↓, and IκBα↑                 | [92]       |
| LPS-induced endotoxemia and lung injury in mice    | Mice (lung)                      | 25, 50, and 75 mg/kg | TNF-α↓, IL-1β↓, and IL-6↓                              | [122]      |
| LPS-induced macrophages in mice                    | Mouse cells                      | 1–100 µg/mL        | iNOS↓, COX-2↓, TNF-α↓, IL-1β↓, IL-6↓, MMP-1↓, MCP-1↓, NF-κB↓, p65↓, IκBα↑, and NO↑ | [127]      |
| LPS-induced RAW 264.7 cells. Inhibitory activity on | Mice (RAW 264.7 cells)           | 1, 10, and 100 μM   | NO↑ and TNF-α↓                                        | [37]       |
| the histamine release by KU812 cells               | KU812 cells                      | 10 to 30 μmol/L    | IL-4↑, IL-13↑, and (IFN-γ) no effect                  | [12]       |
| LPS-induced inflammation in RAW 264.7 cells        | Mice (RAW 264.7 cells)           | NO↓, IL-6↓, and PGE2↓ |                                                       | [33]       |
| P. gingivalis-induced human gingival epithelial (HGE) cells | Human gingival epithelial cells | COX-2↓, IL-6↓, IL-8↓, MMP-1↓, MMP-3↓, PGE-2↓, and IL-4↓ | [125]      |
| Anti-inflammatory effects on                        | Uterine and endometrial epithelial cells of mice | 100 µg/mL | TNF-α↓, IL-1αβ, IL-6, NF-xβ↓, p38↑, p-p38 MAPK↓, ERK↑, JNK↓, and p-p65↓ | [124]      |
| Leptospira interrogans-induced inflammatory response | Mouse model of allergic asthma   | 0.5 mg/kg and 1 mg/kg | SOCS-3↓, SOCS-5↓, and IFN-γ↓ | [126]      |
| Protective effects against                         | Diabetic rats and nondiabetic rats |                  | PAR2↓, IL-1β↓, IL-6↓, TNF-α↓, and TGF-β1↓             | [128]      |
| ovalbumin- (OVA-) induced allergic inflammation    |                                  |                    |                                                       |            |
| All alleviation in hepatic fibrosis function        |                                  |                    |                                                       |            |
| Prevention from atopic dermatitis                  | NC/Nga mice                      | 1.5 mg/kg          | IgE↓                                                  | [87]       |

1↑Upregulation; 1↓downregulation; 1↓inhibition.

Another investigation on LPS-stimulated expression of inflammatory mediators in macrophages has declared the fact that astragalin actively inhibited the expression of proinflammatory mediators via inhibiting NF-κB signaling pathway [123]. Astragalin has been known to halt the MAPK and NF-κB pathways in leptospira-induced uterine and epithelial inflammation in mice [124]. Astragalin has capability to inhibit the production of prostanoid E2 (PGE2) in periodontal pathogen-induced periodontitis, a destructive pathological condition, in human gingival epithelial cells [125]. Astragalin has been investigated to determine the underlying mechanism for its protective effect against ovalbumin-stimulated allergic reactions in mouse models of allergic asthma. Results have declared that it effectively lowers the eosinophil count in lung tissues and inhibited eosinophilia induced by ovalbumin. As a result, IgE, IL-4, IL-5, and IL-13 were retrieved in bronchoalveolar lavage fluid [126]. Purely prepared astragalin inhibited the activity of PGE2 and downregulated the production of cellular nitrite oxide and IL-6 in LPS-stimulated RAW 264.7 cells [33]. Astragalin treatment leads to the inhibition of alveolar destruction, allergic inflammation, and thickening of airways in the ovalbumin-induced inflammatory mouse model [14]. Anti-inflammatory activities of astragalin in different animal models are recorded in Table 2.

3.2. Antioxidant Activity. In living systems, free radicals such as hydroxyl radicals (OH−), superoxide anion (O2−), singlet oxygen (1O2), and ROS are reported to have deleterious impacts on cellular functions. Excessive production of free radicals may affect the balance of prooxidant and antioxidant systems in the body, thus causing various pathological conditions such as arterial hypertension, rheumatism, inflammation, diabetes, cancer, neurodegenerative disorders, and genetic mutations [120]. Researchers have affirmed various plant extracts as natural and infinite treasure of antioxidants. These antioxidants act as free radical scavengers, electron donors, and chelating agents for free catalytic metals in biological systems [75].

Astragalin also inhibits the endotoxin-induced oxidative stress, which can lead to epithelial apoptosis and eosinophilia. It can also act as an antagonizing agent against endotoxin-induced oxidative stress via modulation of LPS-TLR signaling network [129]. Astragalin causes the suppression of 6-hydroxydopamine-stimulated neurotoxicity in Caenorhabditis elegans via modulation of apoptosis-related pathways and alleviation of oxidative stress [130]. Astragalin has capability to improve neural function in the ischemia brain injury model of rats via blocking the apoptosis in the hippocampus region by enhancing the expression of NCam [131] (Table 3).

3.3. Neuroprotective Activity. Disturbance in cerebral redox homeostasis is the main cause of neurodegenerative diseases in humans. Cerebral oxidative stress leads to dopaminergic neuronal cell death and dysfunction. Neuroprotective mechanism of naturally occurring bioactive entities is associated with their free radical scavenging capability generated by neurotoxins and oxidative stress-induced processes in neuronal cells of the brain [133].

Astragalin has been reported to decrease the neurodegeneration in C. elegans stimulated by 6-OHDA and...
increase lifespan of astragalin-treated nematode. It also reduces the ROS levels, inhibits lipid peroxidation, and increases SOD and GPx activities. Furthermore, it is capable of enhancing AChE and reducing the transcript level of proapoptotic gene egl-1 associated with neuronal cell death [130]. In another attempt, the effects of astragalin on CNS were assessed by the application of the leaves extract of Eucommia ulmoides. The extract with high percentage of medicines have been suggested as one of the treatment limitations of their own. Natural products and herbal therapeutics such as hypoglycemic drugs and insulin have by hyperglycemia which is caused by deficit in insulin action or production [139]. Currently available antidiabetic therapies such as hypoglycemic drugs and insulin have limitations of their own. Natural products and herbal medicines have been suggested as one of the treatment increases SOD and GPx activities. Furthermore, it is capable of enhancing AChE and reducing the transcript level of proapoptotic gene egl-1 associated with neuronal cell death [130]. In another attempt, the effects of astragalin on CNS were assessed by the application of the leaves extract of Eucommia ulmoides. The extract with high percentage of medicines have been suggested as one of the treatment limitations of their own. Natural products and herbal therapeutics such as hypoglycemic drugs and insulin have by hyperglycemia which is caused by deficit in insulin action or production [139]. Currently available antidiabetic therapies such as hypoglycemic drugs and insulin have limitations of their own. Natural products and herbal medicines have been suggested as one of the treatment

### Table 3: Antioxidant activity of astragalin in vitro and in vivo.

| Assay                                      | Organism tested | Dose/concentration | Molecular targets | References |
|--------------------------------------------|-----------------|--------------------|-------------------|------------|
| Free radical-scavenging activity           | Mice            | 1, 3, 10, 30, 100, or 300 µg/mL | E-cadherin↑, vimentin↑, Beclin-1↑, LC3A/B↑, EMT↑, and TGF-β1↓ | [107]      |
| Inhibitory activity against autophagy-assOCIated airway epithelial fibrosis | Mice            | 1–20 µM            | TLR-4↓ Eotaxin-1↓ PLCy1↓ PKCβ2↓ p-p22↓ p-47↓ JNK1↓ p38 MAPK1↓ Akt↓ and ERK↓ | [132]      |
| Apoptotic and eosinophilia amelioration    | BEAS-2B cells   | 1–20 µM            | E-cadherin↑, vimentin↑, Beclin-1↑, LC3A/B↑, EMT↑, and TGF-β1↓ | [107]      |
| Suppression of 6-hydroxydopamine-induced neurotoxicity in *Caenorhabditis elegans* | *C. elegans*    | 2.0 mg/mL          | egl-1↑ SOD↑ GPX↑ AChE↑ and p38 MAPK2↓ | [130]      |
| Neuroprotective effect against ischemic brain injury | Wistar rats    | 5 mg/kg and 15 mg/kg | NCam↑ | [131]      |

↑ Upregulation; ↓ downregulation; ^ inhibition.

3.4. Cardioprotective Activity. Myocardial infarction and ischemic heart failure are the leading causes of mortality in the developing countries, and their number is increasing day-by-day. They may result in reperfusion arrhythmias, myocardial stunning, and similar other cardiovascular disorders [16]. An enhanced perception of ischemia reperfusion (I/R) damage provides an innovative approach for new cardioprotective administrations [134]. Regulation of bradykinin, adenosine, opioid, adrenergic, and other G-protein connected receptors have been known to be associated with myocardial protection [135].

Certain epidemiological studies have confirmed that flavonoids stimulate cardioprotective effects against myocardial ischemia [136]. Astragalin, a bioactive flavonoid, was proved to be effective against acute I/R injury in Sprague-Dawley rats as its mechanism of action precedes via diminishing intracellular oxidative stress and apoptosis. The associated mechanism involves decreased expression of MDA, TNF-α, IL-6, ROS, and Bax along with the increased ratio of GSH/GSSG, respectively [137].

3.5. Antiobesity Activity. The term “obesity” can be defined as impaired energy balance that usually results from either enhanced caloric intake and/or reduced energy consumption.
options for diabetes since ancient times. Naturally occurring bioactive chemical entities such as flavonoids, terpenoids, alkaloids, and phenolics have been reported as antidiabetic agents [140].

Diabetic retinopathy (DR) arises due to diabetes mellitus and is one of the most common causes of vision loss. Hyperglycemia leads to overexpression of many biological effectors such as vascular endothelial growth factor (VEGF) which is very crucial for the development of DR. Astragalin derived from A. membranaceus has beneficial effects against hyperglycemia. It helps to prevent DR by decreasing the overexpression of VEGF in cultured murine cells and alleviating the effects caused by high concentration of glucose in the blood [141].

3.8. Antifibrotic Activity. Environmental factors like air pollutants may result in considerable production of reactive oxygen species in the airways. Astragalin isolated from leaves of persimmon and green tea can be effectual in allaying ROS-prompted bronchial fibrosis as it has capability to inhibit auto phagosome formation in the airways [132]. It also alleviates hepatic fibrosis by regulating PAR2 (protease-activated receptor 2) mechanism. AGS regulates proinflammatory cytokines namely IL-6, IL-1β, and TNF-α. It also attenuates the PAR2 signaling expression, and its protective effects are especially prominent in diabetic animal models [128].

3.9. Cosmetic Use. Astragalin glucosides can be used as valuable agents in cosmetics due to their important chemical characteristics. First of all, it inhibits collagenase activity. Collagenase is involved in the hydrolyzation of dermal matrix protein formation as well as wrinkle formation. Secondly, astragalin has an antioxidant activity as it alleviates the free radical species. Thirdly, astragalin controls the pigmentation in the skin caused by melanin [142]. Melanin pigment causes darkening of complexion in skin, eyes, and hair in humans. Nelumbo nucifera (lotus) contains bioactive compounds astragalin and hyperoside in the receptacles which are known to be the melanogenesis inhibitor, thus possibly decreasing the skin darkness [143]. Astragalin along with quercetin is known to possess protective effect against the UV radiations. UV radiations can make the skin of animals prone to various biological responses such as DNA damage, formation of sunburn cells, melanogenesis, pho-toaging, skin cancer, hyperplasia, immune suppression, and edema. UV radiations from the sun can also damage macromolecules in the epidermal layer of animals creating specific changes in the skin, for example, mutations in genes and changes in the immune system. Expression of major CXC chemokines, that is, chemokine ligand 1 (CXCL1) and chemokine ligand 2 (CXCL2), at sites of inflammation within the skin are upregulated after the exposure of skin to UV radiations. These chemokines are the potent stimulators of neutrophil activation which later on produce ROS and leads to oxidative stress. Astragalin, a major flavonoid, can be used as a barrier against UV-induced damage as it is associated with downregulation of CXCL-1 and CXCL-2 in the skin and thus can be used as a photoprotective agent [144] (Table 4).

### Table 4: Cosmetic uses of astragalin.

| Assay                        | Organism tested                          | Dose/concentration       | Molecular targets       | References |
|------------------------------|------------------------------------------|--------------------------|-------------------------|------------|
| Inhibition of melanin secretion | Leuconostoc mesenteroides                | 10 mM                    | MMP-1<sup>¼</sup>        | [142]      |
| Protection against UV damage | Mice (BALB/c) and human keratinocyte cells (HaCaT cells) | 2.5 mg/kg and 0.25 µM/ml | CXCL-1<sup>⁻</sup> and CXCL-2<sup>⁻</sup> | [144]      |

<sup>1</sup> Downregulation; <sup>2</sup> inhibition.

3.10. Antiosteoporotic Activity. Osteoporosis is characterized by structural deterioration of tissues in the bone along with lower bone mass and bone fragility. The main causes of osteoporosis include estrogen deficiency, excess of glucocorticoids, and oxidative stress. Astragalin, an active compound, isolated from crude methanolic extract of the seeds of C. chinensis showed estrogenic activity against osteoporosis, and it is responsible for significant osteoblastic cell proliferation in UMR-106 osteoblastic cells [17].

3.11. Anticancer Activity. Currently, cancer is the second leading cause of mortality worldwide. In spite of advances in the development of new therapeutic preferences for cancer, its ratio is increasing day by day. Every year, almost 7 million people die due to cancer. Lung cancer particularly non-small cell lung cancer (NSCLC) accounts for more than 80% of deaths all around the world today. Therefore, it is necessary to discover new cheap and inexpensive drugs that can ameliorate the antitumor effects and reduce the side effects of generally recommended chemotherapy drugs [145].

Natural phytochemicals that are active constituents of medicinal plants, seeds, fruits, and herbs including polyphenols (flavonoids, terpenoids, and carotenoids) have gained significant recognition for their potential value as therapeutic agents [146, 147]. Much research work has been conducted towards the assessment of phenolic phytochemicals as potent prophylactic agents as they can act on multiple cellular targets. The mechanistic insight into chemoprevention incorporates induction of apoptosis and cell cycle arrest or prohibition of certain cell signaling pathways mostly protein kinases C (PKC), glycogen synthase kinase (GSK), mitogen-activated protein kinases (MAPK), and phosphoinositide 3-kinase (PI3K) leading to abnormal AP-1, COX-2, and NF-κB expressions. Efficacy of chemopreventive agents revert their capacity to counteract with certain up-stream signals that leads to redox imbalances, genotoxic injury, and other situations of cellular stress. Thus, targeting damaged...
molecules along with interrupted signal transduction pathways in cancer epitomize a rational strategy for chemoprevention, and phenolic compounds seem to be auspicious in this aspect [147, 148]. In recent years, flavonoids have drawn developing consideration as powerful anticancer agents against various cancer types [149]. Several investigations on astragalin have explained its anticancer effect due to its promising competency to inhibit proliferation in different cancer cell lines including leukemia (HL-60) [15], hepatocellular (HepG2, Huh-7, and H22) [150], skin (HaCaT, A375P, and SK-MEL-2) [151], and lung (A549 and H1299) cancerous cells [145].

Astragalin heptaacetate (AHA), a therapeutically active flavonoid, induces apoptosis in HL-60 cells through release of cytochrome c into the cytosol. The associated mechanism involves activation of Bax, caspase-3/7, and p38MAPK and intracellular ROS generation along with inhibition of cell signaling pathways JNK/SAPK and ERK 1/2 [15]. Astragalin also prohibits TNF-α-induced NF-κB activation in A549 and H1299 cells. Moreover, AG-triggered cell death is affiliated with increased Bax: Bcl-2 ratio and enhanced cleavage of caspase-3/9 and PARP in conjunction with blockage of PI3K/Akt, MAPK, and ERK 1/2 signaling cascades in a time- and dose-related manner [145]. In hepatocellular carcinoma cells, astragalin (AG) significantly suppressed proliferation both in vitro in HepG2 cells and in vivo in Huh-7 (nude mice) and H22 (Kunning mice) cells via mechanismically inhibiting hexokinase 2 and upregulating miR-125b expression, respectively [150].

Astragalin can be a novel anticancer agent for the cure and prevention of UVB-stimulated actinic keratosis skin lesion by suppressing phospho-MSK1, γ-H2AX, and p38MAPK activation in a time- and dose-related manner in human HaCaT cells in vitro and Balb/c mice in vivo. In another report, astragalin strongly exerted cytotoxic effects in A375P and SK-MEL-2 cancerous cells in a concentration-dependent way through induction of apoptosis. The underlying cell death mechanism involves activation of Bax and caspase-3/9, cleavage of PARP, and downregulation of cyclin D1 and Mcl-1 along with inhibition of Sry-related HMG-Box Gene 10 (SOX10) signaling cascade [151, 152]. The reported data recommend astragalin’s multitargeted activity in preference to single effect that may perform an imperative role towards developing astragalin into potential anticancer drug in future (Table 5).

### 4. ADMET Profiles of Astragalin

ADMET profiles along with biological activity spectra were performed for astragalin based on in-silico tools. The results indicate that astragalin is a potential anticancer agent which is unlikely to present any acute hazard or toxicity. Furthermore, astragalin can be absorbed by human intestines, but it is incapable of penetration to Caco-2 cells. Astragalin has been validated as a novel substrate of p-glycoprotein but it is incapable of penetration to Caco-2 cells. Astragalin has been reported to modulate inflammatory responses by regulating the expression of NF-κB, iNOS, cytokines/chemokines (COX-2, TNF-α, IL-10, and IL-6), MAPK signaling pathways (PGE2, IgE, IL-4, IL-5, IL-13, IL-1β, and IL-6), and PAR2 signaling expression. It also has the capability to alleviate the production of ROS and inhibit the endotoxin-induced oxidative stress (Figure 3). Astragalin is also known to be an inhibitor of ERK-1/2 and Akt signaling; therefore, it is a significant compound against cancer proliferation. In this review paper, we have emphasized on various pharmacological properties of astragalin such as anti-inflammatory, antioxidant, neurological, cardioprotective, antidiabetic, and anticancer. Although several in vitro and in vivo investigations have demonstrated its

### Table 5: Anticancer activities of astragalin in vitro and in vivo.

| Type of cancer | Cell line | Dose/concentration | Molecular targets | References |
|---------------|-----------|---------------------|-------------------|------------|
| Leukemia      | HL-60     | 6 ± 1 μM            | Bax<sup>1</sup>, Bcl-2<sup>2</sup>, caspase-3/7<sup>Act</sup>, JNK/SAPK<sup>4</sup>, and ERK 1/2<sup>4</sup>, H2K<sup>2</sup> and mIr-125B<sup>1</sup> | [150] |
| Hepatocellular| HepG2, Huh-7, and H22 | —                   | p38 MAPK<sup>4</sup>, phospho-MSK1<sup>4</sup>, γ-H2AX<sup>4</sup>, caspase-9/-3<sup>Act</sup>, Bax<sup>8</sup>, PARP cleavage, cyclin D1<sup>1</sup>, Mcl-1<sup>1</sup>, and SOX10<sup>1</sup> | [151, 152] |
| Skin          | HaCaT, A375P, and SK-MEL-2 | 50 and 100 μM/mL | Bax:Bcl-2<sup>1</sup>, caspase-9/-3<sup>1</sup>, p-IKK<sup>β</sup>, NF-κB p65<sup>4</sup>, TNF-α, ERK-1/2<sup>4</sup>, JNK<sup>4</sup>, PI3K/Akt<sup>1</sup>, DDH<sup>4</sup>, DRP<sup>1</sup>, pro-caspase-3/-8<sup>4</sup>, and Bax<sup>1</sup> | [153] |
| Lung          | A549, H1299, H226, H838, H23, H1437, H125, H2009, and H2087 | 5, 40 μg/mL (A549) and 20 μg/mL (H1299) | DDH<sup>4</sup>, DRP<sup>1</sup>, pro-caspase-3/-8<sup>4</sup>, and Bax<sup>1</sup> | [153] |
| Breast        | ZR-75-1, T47D, BT20, MCF-1, and MCF-7 | —                   | DDH<sup>4</sup>, DRP<sup>1</sup>, pro-caspase-3/-8<sup>4</sup>, and Bax<sup>1</sup> | [153] |
| Gastric       | AGS, SC-M1, NUGC-1, NUGC-3, and KOTA-III | —                   | —                 | —          |

<sup>1</sup>Upregulation; <sup>2</sup>downregulation; <sup>3</sup>inhibition.

### 5. Conclusions and Future Perspectives

Astragalin, a natural flavonoid, has been isolated from various traditional medicinal plants such as Cassia alata, Moringa oleifera, Nelumbo nucifera, Cuscuta spp., Radix astragali, Morus alba, and Eucommia ulmoides. Astragalin has been reported to modulate inflammatory responses by regulating the expression of NF-κB, iNOS, cytokines/chemokines (COX-2, TNF-α, IL-10, and IL-6), MAPK signaling pathways (PGE2, IgE, IL-4, IL-5, IL-13, IL-1β, and IL-6), and PAR2 signaling expression. It also has the capability to alleviate the production of ROS and inhibit the endotoxin-induced oxidative stress (Figure 3). Astragalin is also known to be an inhibitor of ERK-1/2 and Akt signaling; therefore, it is a significant compound against cancer proliferation. In this review paper, we have emphasized on various pharmacological properties of astragalin such as anti-inflammatory, antioxidant, neurological, cardioprotective, antidiabetic, and anticancer. Although several in vitro and in vivo investigations have demonstrated its
diversified pharmacological applications, further experimentation along with medicinal chemistry approaches and preclinical trials is still obligatory to uncover the knowledge of its biological and pharmacological applications and their associated mechanisms of actions for the treatment and prevention of several diseases.

Abbreviations

Ache: Acetylcholinesterase  
Bax: Bcl-2 associated protein  
Bcl-2: B-cell lymphoma-2  
COX-2: Cyclooxygenase-2  
CXCL-1: Chemokine-1  
CXCL-2: Chemokine-2  
DAF-16: Abnormal dauer formation  
DDH: Dihydrodiol dehydrogenase  
DRP-1: Dynamin-related protein-1  
E-cadherin: Epithelial cadherin  
EMT: Epithelial to mesenchymal transition  
Eotaxin-1: Eosinophil chemotactic protein  
ERK: Extracellular signal-regulated kinase  
GPX: Glutathione peroxide  
GSH: Glutathione  
HK2: Human kallikrein-related peptidase-2  
IFN-γ: Interferon gamma  
IgE: Immunoglobulin E  
IL-13: Interleukin-13  
IL-1β: Interleukin-1 beta  
IL-4: Interleukin-4  
IL-6: Interleukin-6  
IL-8: Interleukin-8  
iNOS: Inducible nitric oxide synthase  
IkBα: Inhibitor of kappa B alpha  
JNK: c-Jun N-terminal kinase  
LC3A/B: Microtubule-associated protein 1 light chain  
MMP: Mitochondrial membrane potential  
MMP-1: Matrix metalloproteinase-1  
MMP-3: Matrix metalloproteinase-3  
MIP-1α: Macrophage inflammatory protein 2-alpha  
NACam: Neutral cell adhesion molecule  
NO: Nitric oxide  
PAR2: Protease-activated receptor 2  
PGE2: Prostaglandin E2  
PI3K: Phosphoinositide-3  
PKCβ2: Protein kinase C beta-2  
PLOγ1: Phosphoinositide phospholipase C γ1  
SAPK: Stress-activated protein kinase  
SOCS-3: Suppressor of cytokine signaling 3
SOCS-5: Suppressor of cytokine signaling 5
SOD: Superoxide dismutase
SOD: Superoxide dismutase
SOX10: Sry-related HMG-Box gene 10
TGF-β1: Transforming growth factor beta 1
TLR-4: Toll-like receptor 4
TNF-α: Tumor necrosis factor alpha.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This study was supported by the research grant from The Nagai Foundation, Tokyo, Japan (NFT-R4-2017 and NFT-R4-2018) and TWAS-COMSTECH Research Grant (no. 17-180 RG/PHA/AS_C). The authors would also like to thank Higher Education Commission (HEC), Pakistan, for providing access to related papers from various journals.

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