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# Current findings and future prospective of high-value trans Himalayan medicinal plant *Lycium ruthenicum Murr:* a systematic review

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## Abstract

**Background:** The genus Lycium is commercially known for its nutrient dense goji-berries, among these berries, black goji-berries obtained from *Lycium ruthenicum Murr* are highly valued and widely used as traditional medicine in trans-himalayan cold desert Ladakh and as functional food in several countries.

**Methods:** The current collection of data and literature was done by exploring different scientific portals like SciFinder, Google scholar, PubMed, Dictonary of Natural Products, Institute for Scientific Information, Web of Science and Scopus by searching keywords like black goji berry, crystal pearl, and trans-Himalayan plant.

**Results:** Fruits of *L. ruthenicum Murr*, are overwhelmingly enriched in anthocyanins, proanthocyanidins, polysaccharides, spermine and spermidine alkaloids. The presence of these bioactive phyto-chemicals has been linked with reported anti-diabetic, anti-inflammatory, anti-fatigue, anti-atherosclerosis and neuro-protective properties of black goji berries. A unique color of these berries makes them exceptional as compared to other berries.

**Conclusions:** In this article, we have reviewed the variety of high value phytochemicals of *Lycium ruthenicum Murr*, with a special focus on health promoting anthocyanins which will provide an insight to the readers for exploring novel applications of *L. ruthenicum Murr* in field of medicine and food industries.

**Keywords:** Trans Himalayan, *Lycium ruthenicum Murr* , Anthocyanin, Anti-oxidant, Anti-inflammatory, Neuroprotective, Black gojiberry

## Background

For thousands of years in Southeast Asia, more precisely in China, the *Lycium* genus has been a valued source of medicines and nutrients. This genus carries perennial flowering plants in the family Solanaceae and has 97 species and 6 varieties predominantly distributed across South America, South Africa, China and a few species in temperate Europe and Asia [1]. Among them, only twelve species have been studied to date, out of which three species, viz. *L. chinese, L. barbarum* and *L. ruthenicum Murr* are highly valued for their medicinal properties. Due to presence of plethora of biological active compounds, this genus has gained attention in recent years. The berries of *L. barbarum* and *L. chinese* are red colored while those of *L. ruthenicum Murr* are of purple-black color, all these are commonly known as Goji-berry or wolfberry. *L. barbarum* and *L. Chinese* are well- studied plants and have been found to possess various therapeutic properties like anti-glaucoma, immune-regulatory, anti-tumor, anti-oxidant, anti-aging, neuroprotective and blood

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sugar level reducing activities to name a few while *L. ruthenicum Murr* remains a relatively under-studied plant of the genus [2]. Its unique violet-black appearance make it more promising in respect of nutritional food as well as a potent candidate for health promoting effects in world.

The present review compiles available information concerning phyto-fingerprinting, geographical distribution in the Indian Himalayan region, and traditional medicinal uses of *L. ruthenicum Murr* with a special focus on its natural habitat in Jammu, Kashmir and Ladakh regions in India till date, earlier Wang et al [3] studies were mainly focused on Chinese medicinal uses and restricted to China only thus it create our necessity to compile this review aimed at providing comprehensive and current information regarding the pharmacological potentials of *Lycium ruthenicum Murr* based on its geographical location too. The present review critically analyzes the findings of scientific studies conducted on *L. ruthenicum Murr* to date and presents detailed phytochemistry of its bioactive compounds along with their respective pharmacology. For this purpose, a total of 106 scientific references have been studied and compared to compile the present review.

## Habitat and botanical characteristics

The population of *L. ruthenicum Murr* is localized to the areas of central Asia, Turan and generally dispersed in SW Asia, Europe and America. In Asia, it is distributed from China (Gansu, Nei Mongol, Ningxia, Qinghai, N Shaanxi, Xinjiang, Xizang) to Afghanistan, Pakistan, Russia, Tajikistan, Turkmenistan, Uzbekistan and Indian Himalayas [4]. In India only two species, viz. *L. ruthenicum Murr* and *L. barbarum* have been reported date. *L. ruthenicum Murr* is widely distributed in the Trans-Himalayan Ladakh region at an altitude of 3063–3196 m (3435.28 ′ N, 07727.48 ′E) above mean sea level, chiefly growing on roadsides of Hunder and Udmaru areas of Nubra valley where it is locally known as 'Khizer' [5]. The earliest floristic record of *L. barbarum* mentioned that it is an endemic plant of Kashmir, India, and supposed to be the "Wozej Beri" (http://chenabindustries.blogspot.com/2018/07/goji-berry-lycium-barbarum-plant-india.html). *Lycium ruthenicum Murr* is a long-lived, deciduous, perennial and thorny shrub that belongs to the nightshade plant family, i.e. Solanaceae (Fig. 1). It can grow up to 2 m and has small sessile leaves; zig- zagged bending of stems, internodes with short thorns and extensive roots [6–8].

The hermaphrodite funnel- shaped flowers are pale-purple in color and are pollinated by bees (PFAF Plant Database One to two flowers are found on short shoots with 5–10 mm pedicel with the campanulated calyx of the size of 4.5 mm that are irregularly lobed and are ciliated. The seeds of *L. ruthenicum Murr* germinate during the late spring or early summer season, while the bushes

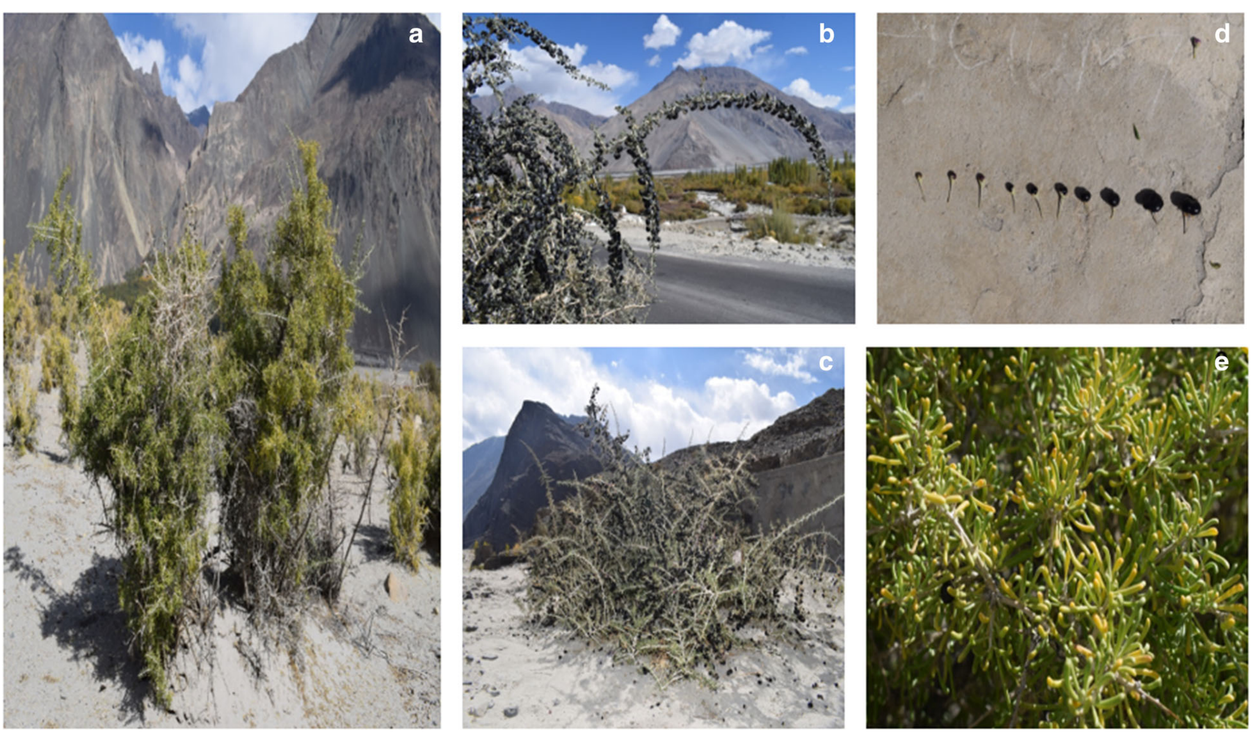



**Fig. 1 a**. *Lycium ruthenicum* Plant **b** & **c**. Plant with ripen Fruits d. Developmental stages of Fruit **e** Close up view of leaves flower during months of June–July and fruits are borne during August–September [5]. The fruits are 6–9 mm long, black-purple ellipsoid berries, commonly called black goji berry (Fig. 1). Being a native of an arid environment, this plant prefers well-drained soil and can grow in nutritionally poor soil which makes it an extremely draught and salt-resistant [9, 10].

## Local and traditional uses

These dark violet purple color berries have been recorded in the classic Tibetan pharmacological book "Crystal Pearl of Materia Medica" and in Chinese medical monographs as Jing Zhu Ben Cao" and "Si Bu Yao Dian" [11]. In India, these berries have been used by Amchi in various herbal formulations as medicine or as a coloring agent [12]. It has been reported that traditionally the fruits have been used as remedies for the treatment of many diseases such as heart diseases, abnormal menstruation, urethral stones, tinea, furuncle, hypertension, menopause, treatment of blindness in camels in mountain communities especially in the Chinese and Tibet medicine systems [11–16]. while leaves are used as diuretic agent to remove blocked urine [17]. The berries have been endorsed as one of the richest known sources of anthocyanins, essential oils, organic acids, trace minerals and polysaccharides have long been used as traditional functional food and used as a herbal tea too (Organic-Natural-Wolfberry-Ruthenicum-Berries/dp/B07P3VGK25).

Even in modern pharmacological research, it's utility as an anti-atherosclerotic, anti-oxidant, cell-mediated immune-enhancer, anti-tumorogenic, hepatic-function protector, anti-fatigue, anti-aging, hypolipidemic and hypoglycemic agent [18]. Although, scientific validation of such medicinal use is missing till date. Most of these traditional uses are based on folk experiences passed over generations without a scientific understanding of the underlying biological mechanism and detailed structure-activity relationship (SAR) of its key bioactive phyto-compounds warranting in-depth scientific studies on biological mechanisms and activities of specific phytoconstituents. Only recently some of the biological activities of berries have been studied in pre-clinical experimental settings discussed below.

## Phytochemical composition and their pharmacological activities

Though limited in number, few research reports are available that describe the phytochemical profile of the *Lycium ruthenicum Murr*, the same has been compiled in Table 1. The reported chemical constituents majorly include anthocyanins, proanthocyaninidins, carotenoids, fatty acids and essential oils, coumarins and cinnamate derivates, polysaccharides, alkaloids and phenolic acids. Among all these, the anthocyanins, which fall under the flavonoids class of compounds, are the most bioactive chemical constituents responsible for most of the reported medicinal properties of *L. ruthenicum Murr* [3]. A comparison of anthocyanin content in *L. ruthenicum Murr* concerning other known sources of anthocyanins is given in Table 2. Their unique color makes them more valuable, due to scarcity of these berries in China; their price is 10 times of red goji berries [30].

**Table 1** Class of Compounds and their percentage of Black Goji Berry

| Class of compound | Percentage | References |
|---|---|---|
| Polysaccharide | 10.3% | [19] |
| Anthocyanins | 2.29% | [20] |
| Polyphenols | 3.94%, | [3] |
| Flavanoids | 4.29% | [3] |
| Proanthocyaninidins | 3.42% | [21] |
| Protein | 10.76%- 14.72%, | [3] |
| Carbohydrate | 69.55% - 77.14% | [3] |
| Fat | 3.90% -6.89% | [3] |
| SFA | 19.43% | [22] |
| Unsaturated fatty acid | 73.00% - 85.29% | [20] |
| MUFA | 21.47% | [22] |
| PUFA | 59.10% | [22] |
| Aminoacids | 7.459% -10.514% | [20] |
| Ash | 6.63% - 10.99% | [20] |
| Carotenoids | 0.084% | [23] |

## Nutritional enrichment

The fruit of *L. ruthenicum Murr* has been reported to contain γ- Vitamin E (VE, (0.0075 mg/g) and δ-Vitamin E (VE) (0.016 mg/g). Also, the oil from *L. ruthenicum Murr*

**Table 2** Anthocyanins content of different plant's Berries

| Source | Content | References |
|---|---|---|
| Black Goji Berry | 9.28–82.58 mg/gDW | [24, 25] |
| Purple sweet Potato | 0.82–1.38 mg/g DW | [26] |
| Cornelian cherry | 2.23 mg/g FW | [26] |
| Blackberry | 10.4–19.8 mg/g FW | [26] |
| Red currant, | 0.07 mg/g FW | [26] |
| Mullberry | 1.2 mg/g DW | [27] |
| Bilberry* | 300 mg/g FW | [28] |
| Blackberry | 82–326 mg/g FW | [28] |
| Blueberry | 25–495 mg/g FW | [28] |
| Cranberry | 67–140 mg/g FW | [28] |
| Lingonberry | 77 mg/g FW | [28] |
| Raspberry | 99 mg/g FW | [28] |
| Redcurrant | 22 mg/g FW | [28] |
| Strawberry | 54 mg/g FW | [28] |
| Black grapes | 4.97–8.42 mg/g FW | [29] |

is known to be rich in α-VE, γ-VE and δ-VE, the reported values of these are 0.1906,1.8939 and 0.045 mg/100 g, respectively. Among these leucine, methionine, isoleucine and phenylalanine are present at a significantly higher level compared to other amino acids Overall, these tiny berries are nutritionally dense and offer a holistic package of health promoting phytonutrients [31, 32].

## Polysaccharides (1–7)

Polysaccharides are the functional components found in the fruits of the *Lycium* genus and have been extensively studied for their therapeutic merits. The polysaccharides in *L. ruthenicum Murr* berries constitute nearly 10 to 17% of the total dry weight [19, 32, 33]. Several polysaccharides from *L. ruthenicum Murr* (LRPs) have been isolated and purified from aqueous extracts of fruits using various methods such as anion-exchange chromatography, gel filtration chromatography, high-performance gel permeation chromatography and high-performance liquid chromatography (HPLC) [3]. Their structural composition has been studied by analytical and chemical methods, including methylation analysis, partial acid hydrolysis, IR (infrared spectroscopy), 1D and 2D NMR (nucleic magnetic resonance) and ESI-MS (electrospray ionization mass spectrometry), gas chromatography. These polysaccharides are complex glycopeptides consisting of hetero-polysaccharides and proteins. Various LRPs isolated and characterized from crude *L. ruthenicum Murr* have been described earlier by Wang et al [3] with their molecular mass, yield and structural composition which includes water-soluble glycoconjugate polysaccharide LRGP1 with molar mass 56.2 kDa, an arabinogalactan-protein LRGP3 with a molecular mass of 75.6 Kd LRP4-A with a molecular mass of $1.05 \times 10^5$ Da, LRP4-A and LRGP5 from fruit extract [34–37]. Researchers had isolated another immunological active polysaccharides named LRLP4-A with a molecular mass of 135 kDa from leaves of *L. ruthenicum Murr* [38]. In our section we have described two more polysaccharides isolated from the fruit extract *i.e* LRP-S2A with a relative molecular weight of 2.65 × 106 Da and an uronic acid content of 41.8%, contained Rha, Ara, Gal, Glc and GlcA in a molar ratio of 1.00: 2.07: 0.57: 2.59: 4.33 was composed of a backbone consisting of 6-O-Me-α-(1 → 4)-D-GlcpA, 2-O-acetyl-α-(1 → 4)-D-Glcp, α-(1 → 2,4)-L-Rhap, β-(1 → 3)-D-Galp andα-(1 → 3,5)-L-Araf, and some branches consisting of 6-O-Me-α-(1 → 4)-D-GlcpA and terminal α-L-Araf [39]. Another homogeneous polysaccharide, LRP3-S1 with a relative molecular weight of 114.8 kDa was purified by anion-exchange chromatography on DEAE Sepharose™ fast flow and sephacryl $S^{-300}$ HR column by Zhang et al. [33]. All LRPs isolated and characterized from *L. ruthenicum* have been compiled in Table 3. Given well- established safety and therapeutic merits of plant-based polysaccharides, *L. ruthenicum Murr* holds promise as an enriched source of bioactive polysaccharides and thus calls for a more intense analytical investigation.

**Table 3** Isolated Polysaccharides in fruit and Leaves of Black Goji berries

| S.No | Polysaccharides | Source | References |
|---|---|---|---|
| 1. | LRGP1 | Fruit | [34] |
| 2. | LRGP-3 | Fruit | [35] |
| 3. | LRP4-A | Fruit | [36] |
| 4. | LRGP5 | Fruit | [37] |
| 5. | LRLP4-A | Leave | [38] |
| 6. | LRP3-S1 | Fruit | [33] |
| 7. | LRP-S2A | Fruit | [39] |

## Alkaloids (8–42)

They are one of the large groups of organic compounds that usually contain at least one nitrogen atom in a heterocyclic ring occurring chiefly in the flowering plants. The presence of nitrogen makes them alkaline. Based upon their respective structures, they can be divided into various types like indoles, quinolines, isoquinolines, pyrrolidines, pyridines, pyrrolizidines, tropanes etc [40]. There have been concerns regarding the presence of certain alkaloids, viz. atropine and hyoscyamine, in other members of the Lycium genus, i.e. *L. halimifolium* and *L. europaeum*, although these compounds are found in concentrations far below their reported toxic doses. However, the presence of such toxic tropane alkaloids has not been reported in *L. ruthenicum Murr* to date. Naturally occurring polyamines are one of the classes of alkaloids that are involved in cell multiplication and its regulation in plants. *L. ruthenicum Murr* is the rich source of spermidine or spermine alkaloids, a pharmacologically important class of alkaloids reported to protect heart from aging, lowering of blood pressure and helpful in fruit ripening. Earlier 24 alkaloids have been reported by Wang et al [3], herein, we have reported some more spermidine or spermine alkaloids from black goji berry. A total of 36 spermine and spermidine has been compiled in Table 4 and Figs. 2 and 3 [43, 44].

## Fatty acids and essential oil (43–78)

Plant-based fatty acids and essential oils are always been valued for their pharmacological utilities such as improving immunity, brain health, mood, cell signaling regulation and reducing inflammation etc. Chi et al [22] studied the lipophilic compound composition of *L. ruthenicum Murr* seed and fruit essential oil in the samples collected from the Qinghai-Tibetan Plateau in China. Both the essential oils were shown to contain saturated, monounsaturated (MUFA), and polyunsaturated fatty acids (PUFA) with a predominance of linoleic, oleic

**Table 4** Identified Alkaloids in Black goji berry

| Sr.No | Alkaloids | References |
|---|---|---|
| 8. | N,N-bis (dihydrocaffeoyl) spermine | [41] |
| 9. | tris-(Dihydrocaffeoyl) spermine | [41] |
| 10. | $N^1$,$N^{14}$-bis-(Dihydrocaffeoyl) spermine | [18, 41] |
| 11. | N-Caffeoylspermidine | [18] |
| 12. | $N^1$,$N^{10}$-bis-(Caffeoyl) spermidine hexose | [18] |
| 13. | $N^1$,$N^{10}$-bis-(Caffeoyl) spermidine dihexose | [18] |
| 14. | $N^1$-Caffeoyl-$N^{10}$-dihydrocaffeoyl spermidine hexose | [18, 41] |
| 15. | $N^1$-Dihydrocaffeoyl-$N^{10}$-caffeoyl spermidine | [18] |
| 16. | $N^1$-Caffeoyl-$N^{10}$-dihydrocaffeoyl spermidine | [18] |
| 17. | $N^1$-Dihydrocaffeoyl-$N^{10}$-coumaroyl spermidine | [18] |
| 18. | 7′-O-[β-D-glucopyranose]-$N^1$,$N^{10}$ didihydrocaffeoyl-spermidine | [42] |
| 19. | 7′-O-[β-D-glucopyranose]-$N^1$-dihydrocaffeoyl-$N^3$-caffeoylspermidine | [42] |
| 20. | 7′-O-[β-D-glucopyranose]-7″-O-[β-D-glucopyranose] -$N^1$- dihydrocaffeoyl-$N^3$-caffeoyl- spermidine | [42] |
| 21. | $N^1$-caffeoyl-$N^3$-dihydrocaffeoyl spermidine | [3] |
| 22. | N,N-bis (dihydrocaffeoyl) spermidine hexoside | [3] |
| 23.. | (dihydrocaffeoyl) caffeoyl spermidine hexoside | [3] |
| 24. | N,N-dicaffeoyl-spermidine | [3] |
| 25. | Caffeoyl (dihydrocaffeoyl) spermidine isomers | [3] |
| 26 | N-Caffeoyl, N′-dihydrocaffeoyl spermidine dihexose | [3] |
| 27. | Lyrium spermidine A | [18] |
| 28. | N-Feruloylagmatine | [18] |
| 29 | N-Monocinnamoyl-putrescine | [3] |
| 30. | N1 –caffeoyl spermidine | [43] |
| 31. | N10-dihydrocaffeoyl spermidine hexose | [43] |
| 32. | N1 -Dihydrocaffeoyl | [43] |
| 33. | N10 - caffeoyl spermidine hexose | [43] |
| 34. | N1, N10-dihydrocaffeoyl spermidine hexoside | [43] |
| 35. | N1,N10-bis (dihydrocaffeoyl)spermidine | [44] |
| 36. | N-trans-coumaroyltyramine | [44] |
| 37 | N-trans-feruloyltyramine | [44] |
| 38. | N-trans-feruloyl 3′-O-methyldopamine | [44] |
| 39. | N-trans-feruloyloctopamine | [44] |
| 40. | N-cis-coumaroyltyramine | [44] |
| 41. | N-cis-feruloyltyramine | [44] |
| 42. | N-cis-feruloyloctopamine | [44] |

and palmitic acids. It is worth mentioning here that linoleic acid is an essential fatty acid with a key role in the eicosanoid synthesis pathway as a precursor of arachidonic acid [47]. Earlier review had compiled 25 fatty acids and essentials oils, we have reported total of 36 fatty acids and essentials oils where the key fatty acids from *L. ruthenicum Murr* oil included linoleic, oleic, palmitic, linolenic and stearic acids which together comprised 95.59% of the total fatty acids. According to literature the comparative ratio of PUFAs, MUFAs and SFs in berries and seed oil are (59.10%: 63.99%), (21.47%: 21.76%),(19.43%: 14.26%) [45, 46] (Fig. 3 and Table 5).

### Phytosterols (79–87)

Phytosterols are cholesterol-like molecules found in all plant foods, with the highest concentrations occurring in vegetable oils. They are absorbed only in trace amounts but inhibit the absorption of intestinal cholesterol including recirculating endogenous biliary cholesterol, a key step in cholesterol elimination. The sterol composition has been used as an important marker to mark the geographical locations of various goji berry samples (including *L. chinense* and *L. barbarum*) using linear discriminant analysis (LDA) and principal component analysis (PCA) [48]. In our study, we have compiled total nine phytosterols isolated from seed oil of *L.ruthenicum Murr* (Table 6 and Fig. 4), which were not analyzed in previous studies [46]. The total content of phytosterol was approx 489.2 mg/100 g samples of black gojiberries which majorly consisted of stigmasterol, campesterol and β-sitosterol. Additionally, the Vitamin A and E contents were 0.3 mg/100 g and 46.3 mg/100 g in tested samples, proposing the blackberry vegetable oil worth exploration for further development.

### Carotenoids (88–93)

Carotenoids are a class of phytonutrients ("plant chemicals") belonging to the terpenoid family, called tetraterpenoids. They are yellow, orange and red- colored pigments that are produced by plants, algae, several bacteria and fungi. Zeaxanthin, β-cryptoxanthin, β-carotene are some of the common carotenoids which have been reported from *L. ruthenicum Murr* and play a crucial antioxidant function of deactivating free radicals such as single oxygen atoms that can damage cells by reacting with other bio-molecules. As expected owing to its black-purple color, the black goji berry from Qinghai Province in China showed a much lower carotenoid content (1.51–3.19 μg/g) compared to red goji berry (212.24–233.08 μg/g) [23, 24]. In a very interesting study by Liu Y et al. [49], it was shown that undetectable carotenoid content in black goji berry is due to lack of chromoplast biosynthesis and not due to inactivation of carotenoid biosynthesis pathway during fruit ripening. Since, chromoplasts are the reservoirs for colored pigments, in absence of these in *L. ruthenicum Murr* fruits and overexpression of carotenoid cleavage dioxygenase 4 enzyme leads to continuous degradation of carotenoids. The carotenoids reported from gojiberries have been compiled in Table 7 and Fig. 5.

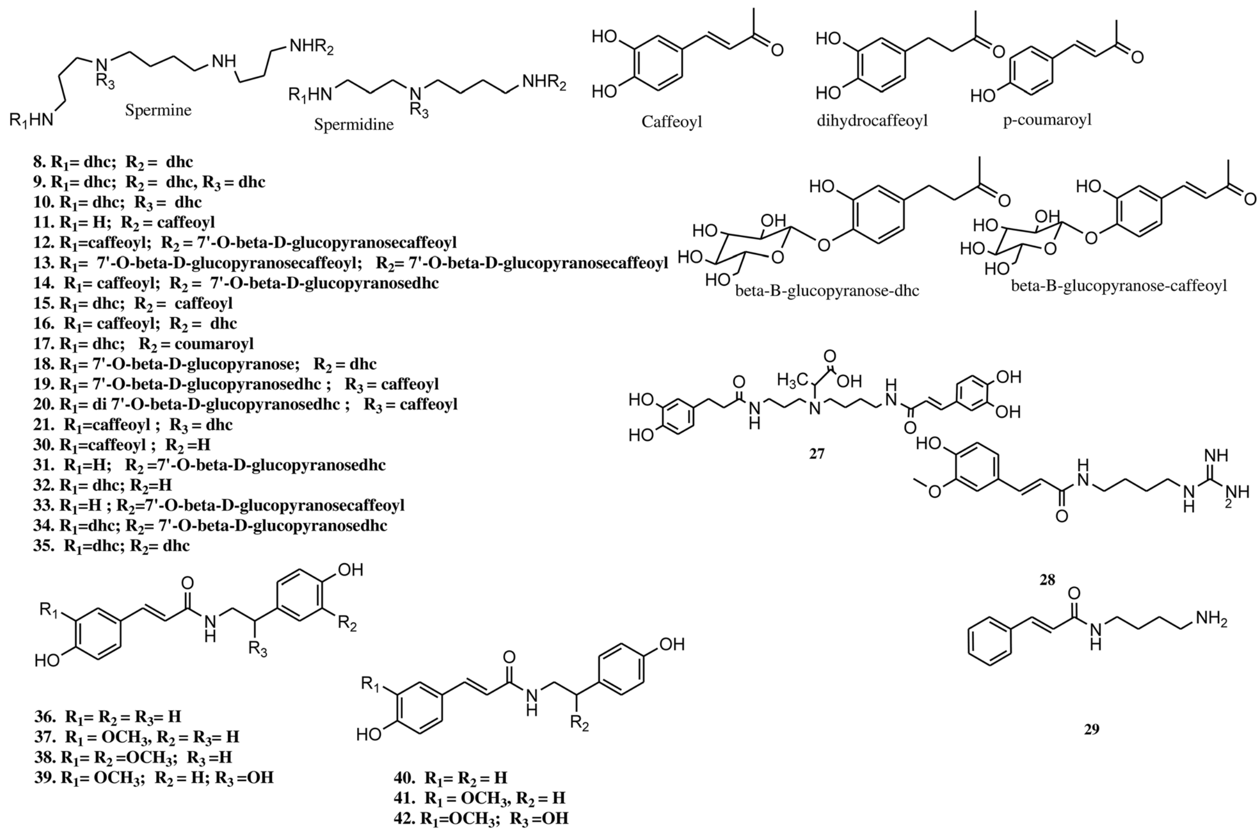



**Fig. 2** Representative Structure of Alkaloids

### Phenolic acid and flavonoids (94–133)

As discussed in detail in forthcoming sections, the black goji berries have been repeatedly shown to possess significantly higher anti-oxidant properties than other closely related gojiberries, i.e. *L. barbarum* and *L. chinense* despite their much lower carotenoid contents. Research studies have established the supremacy of phenolic compounds, such as condensed tannins, phenolic acids and flavonoids as contributors to plant's antioxidant capacities [50]. Different extraction methods have been followed for the detection of different phenolic acids in *L. ruthenicum Murr* samples such as ultrasonic-assisted extraction using the surface methodology, UPLC-Q-Orbitrap MS etc. Observations of significantly higher total phenolic content (8.33 mg GAE/g), total flavonoid content (11.09 mg CAE/g) and condensed tannins (20.87 mg CAE/g) in black goji berry samples than in red goji berry (3.16 mg GAE/g, 2.83 mg CAE/g and 1.08 mg CAE/g) respectively is a highly convincing [24, 51]. Since retention of these superior antioxidant properties in dried black goji berries is a highly desired feature for its commercialization as a functional food, the effect of different drying methods on the content of polyphenols has been extensively studied by several researchers [52, 53]. It has been concluded that the contents of total polyphenols remain highest by the air-drying method as compare to other methods viz. *low*-temperature oven drying and vacuum freeze- drying. Table 8 gives details of the forty phenolic acid and flavonoids detected in black goji berry to date and their respective structures have been shown in Fig. 6.

### Coumarins and Cinamate derivatives (134–136)

Coumarins act as an antioxidants, enzyme inhibitors, and precursors of toxic substances. In addition to biological activities, they are used as additives in food, cosmetics and optical brightening agents [55]. The phytochemical investigation of ethyl acetate extract of black goji berry has lead to the isolation of two coumarins (Scopoletin and Esculetin) and Methyl-2-hydroxy-4-undecanoxy-trans- cinamate which was characterized by $^{1}$H-NMR, $^{13}$C-NMR and FT- IR spectroscopic data, MS spectrometry, elemental analysis and by comparison with the literature values [56]. Table 9 gives the details of these derivatives and structures are described in Fig. 7.

### Anthocyanins and Proanthocyanidins (137–185)

The most important bioactive constituents of *L. ruthenicum Murr* are anthocyanins which are a large family of naturally occurring water-soluble plant pigments

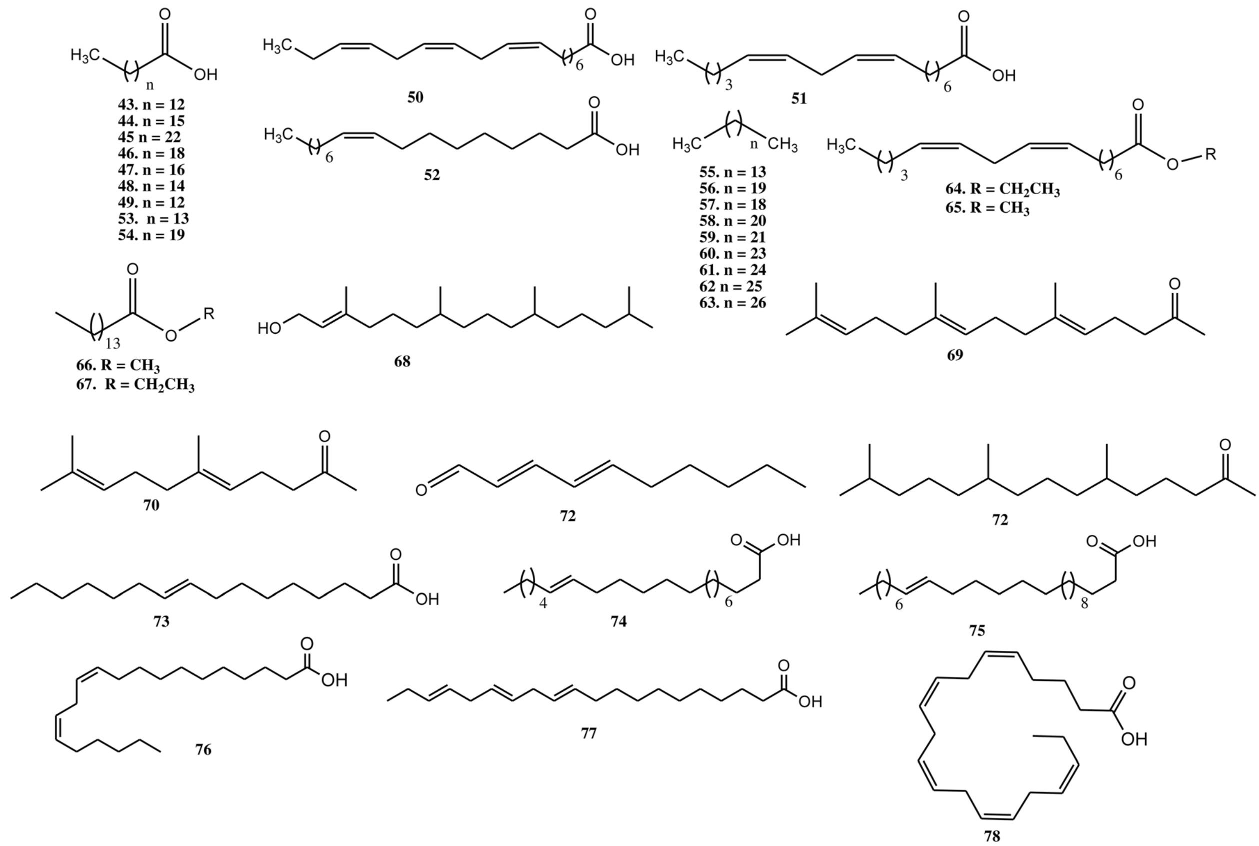


**Fig. 3** Representative Structure of fatty acid and essential oils

including glycoside or acyl glycoside anthocyanidins. They belong to the flavonoids class of compounds. They are found in the vacuolar sap of the epidermal tissues of fruits and flowers. These pigments belong to the most common class of phenolic compounds that share the same basic flavonoid structure with a positively charged oxygen atom at the c-ring of the structure connected with sugar moieties [57]. These sugar moieties are primarily monosaccharides and disaccharides like glucose, rhamnose, galactose, arabinose, sambubiose, rutinose, and sophorose, which are further acylated by organic acids like acetic acid, oxalic acid, phenolic acids such as p-coumaric acid, p-cinnamic acid and ferulic acid etc. The core structure of all anthocyanins remains a phenolated benzopyran referred to as flavylium cation (2-phenylchromenylium) which is described as a C6-C3-C6 skeleton. These pigments are responsible for the blue, purple, red and intermediate colours based on the pH of the microenvironment. They are widely used as nutraceuticals and found in our daily diets especially in berries, thus are extensively consumed by humans among all the flavonoids [58, 59].

These berries are also an affluent source of health-promoting proanthocyanidins and claimed to be richer than malts and hops. A recent study revealed that on addition *L.ruthenicum Murr* berries in beer improved the content of proanthocyanidin from 10 to 68 mg/L in finished beer, and the total polyphenol content in beer was increased from 246 to 457 mg/L [21].

Although the total flavonoid content in *L. ruthenicum Murr* is lower as compared to *L. chinense* and *L. barbarum* but its anthocyanin content is higher. In fact, in case of *L. barbarum*, anthocyanins have not been detected at any stage of the fruit development [60]. Among the chemical constituents of *L. ruthenicum Murr* fruit, the most well- researched component is the group of water-soluble anthocyanins, which are estimated to comprise approx 2.3% of the dried fruits [61]. It has been claimed that black gojiberries are one of the highest anthocyanin- containing natural sources with a maximum reported content of 24.04 ± 0.07 mg/g [43]. Several anthocyanins have been isolated and purified from *L. ruthenicum Murr* berry extracts by various extraction methods such as ultrasound-assisted aqueous two-phase extraction (UA-ATPE) and other analytical techniques such as D-101 resin- based column chromatography and high-performance liquid chromatography (HPLC) [25, 42, 62–64]. Ealier total 38 anthocyanins have been

**Table 5** Identified fatty acid and Essential Oil content of Black Goji berries

| Sr. No. | Fatty acid and Essential Oil | Content Percentage (fruits) | Content Percentage (seed) | References |
|---|---|---|---|---|
| 43. | Myristic acid | 0.14 | 0.04 | [22] |
| 44. | Margaric acid | 0.29 | – | [22] |
| 45. | Tetracosanoic acid | 0.47 | 0.02 | [22] |
| 46. | Arachidic acid | 2.48 | 0.21 | [22] |
| 47. | Stearic acid | 3.56 | 1.40 | [45] |
| 48 | Heptadecanoic acid | – | 0.07 | [22] |
| 49. | Pentadecenoic acid | 0.01 | 0.01 | [22] |
| 50. | Linolenic acid | 4.99 | 6.60 | [45] |
| 51. | Linoleic acid | 59.38 | 74.56 | [45] |
| 52. | Oleic acid | 20.70 | 11.82 | [22] |
| 53 | Palmitic acid | 12.49 | 4.88 | [22] |
| 54. | Docosanoic acid (Behenic acid) | – | 0.06 | [46] |
| 55. | Hexadecane | 0.8 | – | [3] |
| 56. | Docosane | 1.5 | – | [3] |
| 57. | Heneicosane | 0.9 | – | [3] |
| 58. | Tricosane | 2.5 | – | [3] |
| 59 | Tetracosane | 3.9 | – | [3] |
| 60. | Hexacosane | 7.0 | – | [3] |
| 61. | Heptacosane | 14.3 | – | [3] |
| 62 | Octacosane | 5.2 | – | [3] |
| 63. | Nonacosane | 6.2 | – | [3] |
| 64. | Ethyl linoleate | 10 | – | [3] |
| 65. | Methyl linoleate | 5.6 | – | [3] |
| 66. | Methyl hexadecanoate | 4.5 | – | [3] |
| 67. | Ethyl hexadecanoate | 5.8 | – | [3] |
| 68. | Phytol | 3.0 | – | [3] |
| 69. | Farnesylacetone | 4.6 | – | [3] |
| 70. | (E)-Geranylacetone | 1.1 | – | [3] |
| 71. | (E,E)-2,4-Decadienal | 0.8 | – | [3] |
| 72. | Hexahydrofarnesylacetone | 0.8 | – | [3] |
| 73. | Palmitoleic acid | 0.76 | 0.12 | [22] |
| 74. | cis-10-Heptadecenoic acid | – | 0.04 | [22] |
| 75. | cis-11-Eicosenoic acid | – | 0.04 | [22] |
| 76 | cis-11, 14-Eicosadienoic acid | – | 0.02 | [22] |
| 77. | cis-11, 14, 17-Eicosatrienoic acid | – | 0.06 | [45] |
| 78. | n-3 cis-5, 8, 11, 14, 17-Eicosapentaenoic acid | – | 0.01 | [45] |

discussed by Wang et al [3], in our study we compiled total 49 anthocyanins included anthocyanidin with their respected structures [65, 66] (Table 10 and Fig. 8). These anthocyanins are responsible for the organoleptic flavour of the black-purple colored *L. ruthenicum Murr* fruits. The predominant anthocyanin is petunidin 3-O-[6-O-(4-O-(trans-p-coumaroyl) -α-L-rhamnopyranosyl) -β-D-glucopyranoside] 5-O-[b-glucopyranoside, accounting for the largest proportion of anthocyanins in wolfberry fruits, although the contents varies in samples obtained from different geographical locations [25, 42, 64]. The total anthocyanins content determined by the pH differential method ranged from 9.28 ± 1.19 to 82.58 ± 0.95 mg C3GE/ g DW. Five anthocyanidins and five anthocyanins were qualitatively and quantitatively analyzed by Zhang et al [65] among these, 10 constituents (delphinidin-3-glu, cyanidin-3-glu, petunidin-3-glu, peonidin-3-glu, malvidin-3-glu, delphinidin, cyanidin,

**Table 6** Identified phytosterols of Black Goji berries

| Sr. No. | Phytosterol | References |
|---|---|---|
| 79. | 24-methylenecholesterol | [46] |
| 80. | Campesterol | [46] |
| 81. | Stigmasterol | [46] |
| 82. | dihydrolanosterol | [46] |
| 83. | 24-methyldesmosterol | [46] |
| 84. | β-sitosterol | [46] |
| 85. | Δ5 -avenasterol | [46] |
| 86. | Cycloartenol | [46] |
| 87. | Δ7- avenasterol | [46] |

petunidin, pelargonidin and malvidin) were detected. Anthocyanins are well recognized to promote health benefits owing to their potent anti-oxidative, anti-inflammatory, anti-carcinogenic, cardio-protective and neuroprotective effects [70, 71].

## Reported biological activities of *L. ruthenicum Murr* fruits

As it has already been discussed that *L.ruthenicum Murr* is rich in many biological active natural compounds which leads its potential towards many pharmacological activity like antioxidant activity due to presence of abundant of polyphenols, anti-fatigue effect due to existence of polysaccharides etc. So, herein we have categorized and described different biological activity reported from *L.ruthenicum Murr* in depth.

### Anti-oxidant effect

The anti-oxidant properties of *L. ruthenicum Murr* berries have been most extensively worked out by various researchers in in-vitro and in-vivo study models, especially of the berry extracts, which are known to be rich in anthocyanins content [41, 63, 68, 72–74]. These pigments exhibit a noticeable inhibition of lipid oxidation induced by free radicals owing to their strong free radical scavenging activities. *L. ruthenicum Murr* has higher antioxidant potential as compared to *L. barbarum*, most obviously owing to a higher anthocyanin content of *L. ruthenicum Murr* in comparison with *L. barbarum* [24, 51, 75]. Major constituents that were found to be responsible for anti-oxidant properties in several studies are rutin, chlorogenic acid, p-coumaric acid, caffeic acid, syringic acid, dhc-caffeoyl spermidine isomer, quercetin-o-rut, kaempferol-o- rut, isorhamnetin-o-rut, ascorbic acid, lycium spermidine A, tocopherols, carotenoids, anthocyanins, polysaccharides [54, 61, 68]. In general, plants with higher TPC and TFC show stronger antioxidant activity since there is a positive correlation between total polyphenols and positive findings in DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2′-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid) assays [76]. In *Lycium* plant, the TPC was found to range from 698.14 ± 27.15 to 1311.10 ± 80.05 mg GAE per 100 g FW, which was significantly higher than those of bayberry fruit extracts (360.3–446.1 mg/100 g FW) and black berry extracts (261.9–929.6 mg per 100 g FW) [68]. The DPPH free radical- scavenging activity, ABTS, FRAP

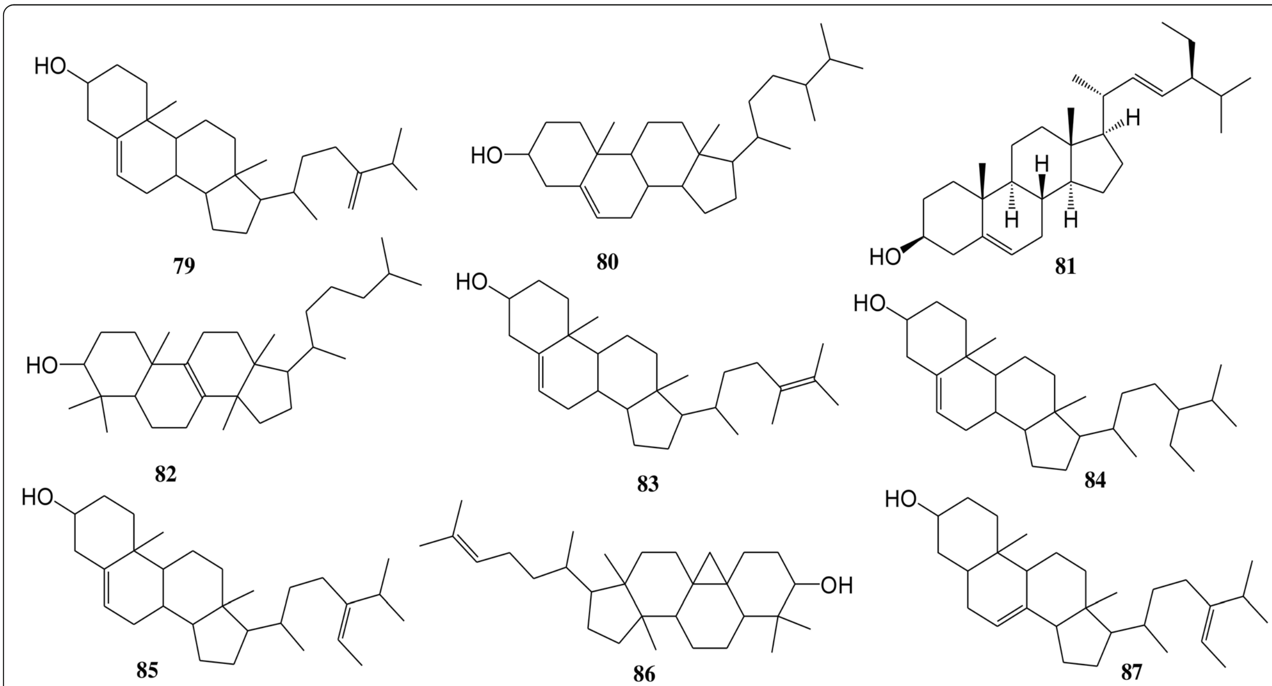



**Fig. 4** Representative Structure of Phytosterols

**Table 7** Carotenoids content of Red and Black Goji berries

| S.No | Carotenoids | Black goji berry | Red Goji berry | References |
|---|---|---|---|---|
| 88. | Lutein | 10.5 ± 0.1 | 52.7 ± 0.2 | [24] |
| 89. | B-Cyptoxanthin | 8.6 ± 0.1 | 739.8 ± 9.6 | [24] |
| 90. | Zeaxanthin | 17.01 ± 0.2 | 9306 ± 111.2 | [24] |
| 91. | Neoxanthin | 265.5 ± 2.6 | 15.6 ± 1.1 | [24] |
| 92. | β-Carotene | 18.8 ± 0.9 | 413.9 ± 3.5 | [24] |
| 93. | Zeaxanthin dipalmitate | 0.031 | 0.214 | [23] |

values of fruit extracts were 49.65 ± 3.1, 47.8 ± 6.6, 56.3 ± 6.9 uM TE/g FW respectively. The chlorogenic acid (112.5 ± 8.4 μg/g FW) was the most abundant phenolic acid found in *Lycium* [77]. Recently, Fatty acids and mineral contents of *L. ruthenicum Murr* have showed antioxidant activity against isoproterenol-induced acute myocardial ischemia in mice reported by Nzeuwa et al [45]. The most bioactive constituent, anthocyanin, has been reported to possess an inhibitory effect on tyrosinase monophenolase with $IC_{50}$ = 1.483 ± 0.058 mg/mL by Shen et al. [78]. Petunidin3-O-[6-O-(4-O-(trans-p-coumaroyl)-a-L-rhamnopyranosyl)-b-D-glucopyranoside]-5-O-[b-Dglucopyranoside] which belongs to class of anthocyanins isolated from *L. ruthenicum Murr* exhibited higher scavenging activities against ABTS, DPPH and superoxide radicals than the crude extract of anthocyanins. Moreover, this compound has a significant effect on inhibition of the reactive oxygen damage induced by $H_2O_2$ in PC12 cells, reflecting in the recovery of plasma membrane integrity, decreased production of MDA, and increased secretion of antioxidant enzymes (glutathione peroxidase: 146.24 ± 7.25 mg/protein, superoxide dismutase: 91.83 ± 5.81 mg/protein and catalase: 23.45 ± 3.01 mg/protein) vitamin E as a positive control [62]. Chinese researchers have patented black goji berry as a natural composite PCT Int. Appl. (2017). Liu et al [79] had studied the antioxidant scavenging activity of *L. ruthenicum Murr* seed oil by using assays based on three kinds of radicals (DPPH·, ·OH and O2·) and lipid peroxidation and found that oil had the potential to be a novel antioxidant agent for use in the field of food, pharmaceuticals and cosmetics. Wang et al. [80] has proposed that in vitro gastrointestinal digestion may enhance the biological activities of anthocyanins especially for antioxidant activity and α-glucosidase inhibition.

### Anti-inflammatory effect

Inflammation is a well-established cause as well as the effect of the plethora of human diseases, thus the need for dietary as well as pharmaceutical anti-inflammatory entities remains unmet to date. Since *L. ruthenicum Murr* is naturally packed with potent anti-inflammatory phytocompounds (*esp* polysaccharides and polyphenols), the in-vitro and in-vivo efficacy of crude extracts of black goji berry fruits has been evaluated in several animal models of inflammatory diseases. Polysaccharides from natural sources are known to be very potent anti-inflammatory bio-molecules [81, 82]. In-vitro anti inflammatory action of isolated water-soluble arabinogalactan polysaccharide from *L. ruthenicum Murr*, LRGP3 has been

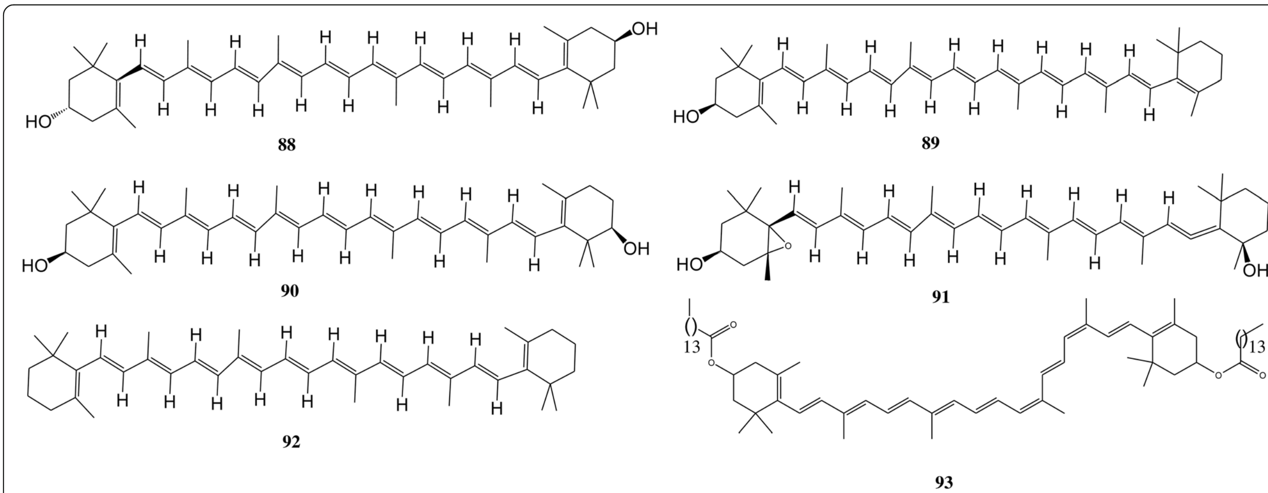



**Fig. 5** Representative structure of carotenoids

**Table 8** Identified Phenolic acid and Flavonoids of Black goji berry

| Sr. No. | Phenolic acid and Flavonoids | References |
|---|---|---|
| 94. | Ampelopsin glucoside | [18] |
| 95. | Catechin | [54] |
| 96 | Quercetin | [3] |
| 97 | Myricetin | [3] |
| 98. | Quercetin-3-O-rutinoside/ Rutin | [18, 41] |
| 99. | Kaempferol | [3] |
| 100. | Kaempferol-O-rutinoside | [41] |
| 101. | Isorhamnetin-O-rutinoside | [41] |
| 102. | Quercetin-O-rutinoside-hexose | [41] |
| 103 | Quercetin-rhamno-dihexoside | [3] |
| 104 | 4-Caffeoylquinic acid | [18] |
| 105 | 4,5-di-O- caffeoylquinic acid | [41] |
| 106 | trans- caffeoylquinic acid | [41] |
| 107 | 1,3-dicaffeoylquinic acid | [18] |
| 108 | 3,4-di-O- caffeoylquinic acid | [41] |
| 109 | 3,5-di-O- caffeoylquinic acid | [41] |
| 110 | trans-neo- caffeoylquinic acid | [41] |
| 111 | trans-crypto- caffeoylquinic acid | [41] |
| 112 | 4-(p-cumaroyl)-methyl-L- rhamnoside | [3] |
| 113 | Caffeic acid | [54] |
| 114 | p-Coumaric acid | [3] |
| 115 | Ferulic acid | [3] |
| 116 | Vanillic acid | [3] |
| 117 | Protocatechuic acid | [3] |
| 118 | Syringic acid | [54] |
| 119 | Chlorogenic acid | [3, 18, 41] |
| 120 | Gallic acid | [54] |
| 121 | Phloretin | [53] |
| 122 | Protocatechuate | [53] |
| 123 | Syringate | [53] |
| 124 | Ellagic acid | [53] |
| 125 | Naringenin | [53] |
| 126 | ruthenicunoid A | [44] |
| 127 | proanthocyanidins-B2 | [52] |
| 128 | O-hydroxybenzene acetic acid | [52] |
| 129 | 2,4-dihydroxybenzoic | [52] |
| 130 | proanthocyanidins-A2 | [52] |
| 131 | veratronic acid | [52] |
| 132 | Naringin | [52] |
| 133 | Hesperidin | [52] |

investigated by Peng et al. [37]. The authors reported that LRGP3 could inhibit the expression of iNOS, production of NO and inflammatory cytokines in RAW264 cells and proposed the anti-inflammatory activity to be mediated by the NF-β-iNOS-NO signaling pathway. A metabolite of LRGP3, i.e. LRGP3-AF, has immune effectors properties viz. significant complement-fixing and macrophage stimulation activities. The galactan backbone of this polysaccharide is shown to be essential for its immunomodulatory activity [83].

The enrichment of anthocyanins in black gojiberry makes it a promising subject for anti-inflammatory activity exploration. In a hyperlipidemia atherosclerosis animal model, *L. ruthenicum Murr* anthocyanins (doses of 100, 200, 400 mg/kg fed for 6w) have shown significant improvement in lipid profile, percent aortic plaque area and severity of inflammatory damage in aorta, heart and liver tissue which were promising in comparison to simvastatin drug group [84]. Further, Shu and Hou [85] also endorsed the anti-inflammatory potential of anthocyanin extract of *L. ruthenicum Murr* in a rat model of carbon tetra-chloride induced hepatic injury. Oral administration of 30 mg *L. ruthenicum Murr* extract for 7 days, led to significant decrease in the levels of ROS, SGOT and SGPT and pro- inflammatory markers including NO, ROS, IL-1 and IL-6. The Plausible mechanism of action of anthocyanins via RAGE/NF-κB/JNK pathway has been explained by Chen S et al [69] in their rat model of d-galactose induced memory impairment. In the same study, it has been shown that these black gojiberry anthocyanins could significantly downregulate inflammatory markers, tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF-κB) and interleuin-1-β (IL-1β) which are hallmarks of inflammatory diseases. Further, in a separate study, *L. ruthenicum Murr* ethanol extract inhibited colonic inflammation by regulating mitogen-activated protein kinase (MAPK) pathways and downregulating NF-κB levels, proposing these black gojiberry as a promising functional food for the management of inflammatory bowel disease (IBD). This in-vivo study was conducted in rat model of dextran sulfate sodium- induced colitis wherein supplementation with berry extracts could suppress activation of (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and regulate inflammation-inducing immune cell infiltration [86].

Supplementation with *L. ruthenicum Murr* has shown promise in a pre-clinical animal model of western diet-induced fatty liver disease. The extract-treated animal group showed reduced triglyceride accumulation and reduced hepatic inflammation [87]. Although in this study, supplementation could not influence the body weight, in a separate study by Yin

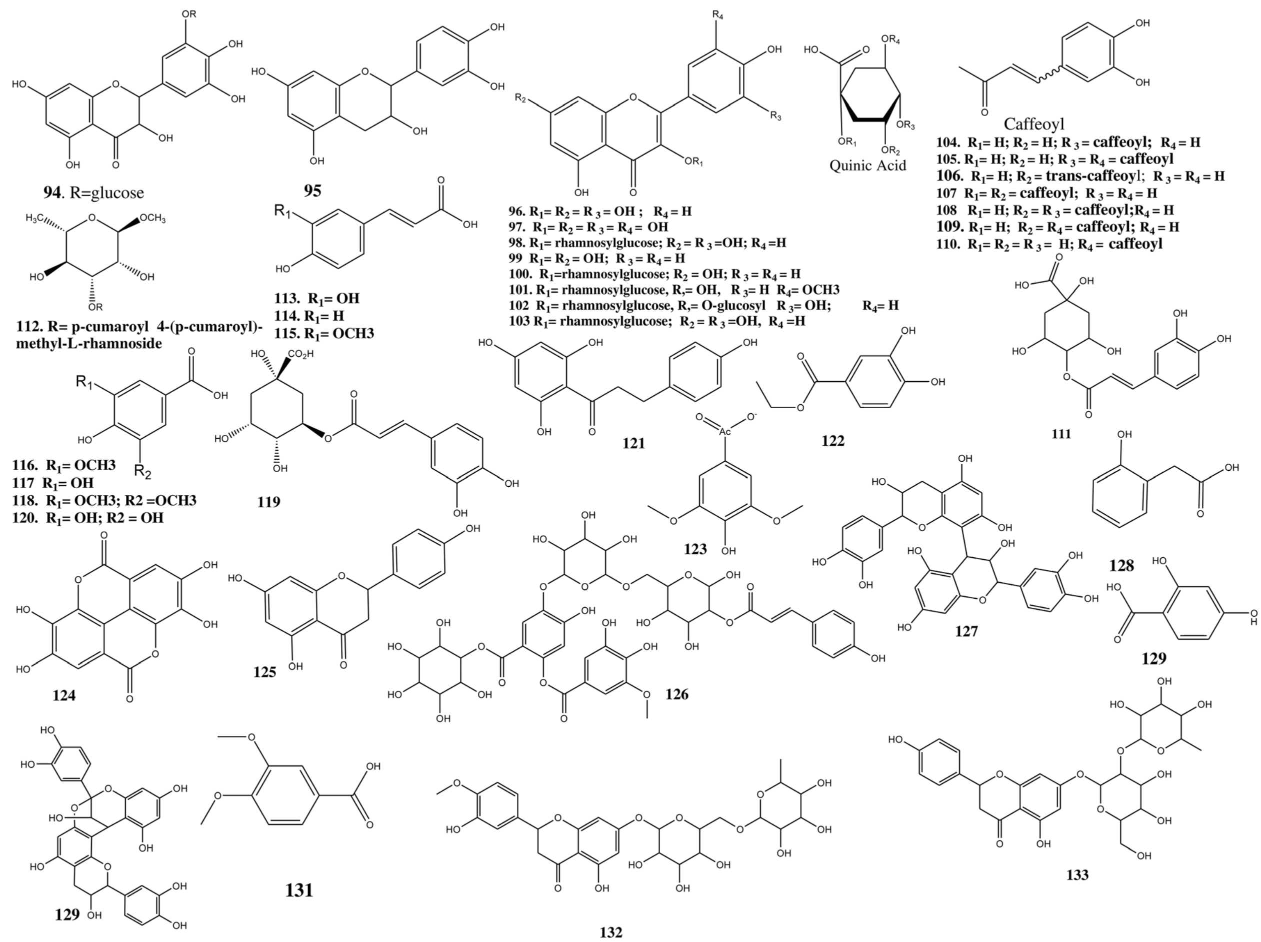



**Fig. 6** Representative Structure of Phenolic acid and Flavonoids

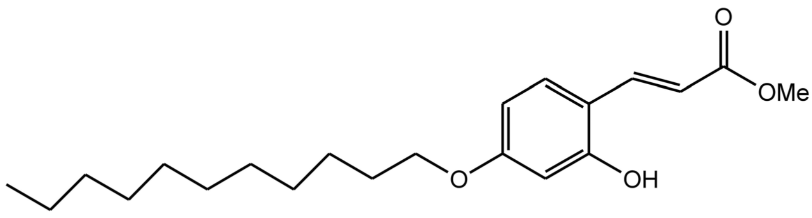
et al. consumption of anthocyanin-rich extract of *L. ruthenicum Murr* was shown to be cause significant reduction in body weight and decrease in the Lee's index along with elevation of serum HDLC, fecal fatty acid content, SOD activities besides reduction in MDA and hepatic lipids. Anti-inflammatory efficacy was shown with marked down-regulation of established pro-inflammatory markers; TNF-α, IL-6, NF-κB, IFN-γ and iNOS. The authors claimed that black wolfberry anthocyanins potentially alleviate diet-induced obesity by regulating accelerating fat decomposition, inflammation, oxidative stress [88].

**Table 9** Coumarins and Cinamate derivatives

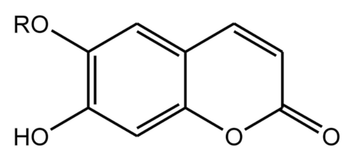
| S.No | Coumarins and Cinamate | References |
|---|---|---|
| 134. | Methyl-2-hydroxy-4-undecanoxy-trans- cinamate | [57] |
| 135. | Scopoletin | [57] |
| 136. | Esculetin | [57] |

## Neuroprotective effects

Neurodegenerative diseases like Alzheimer's are associated with progressive cognitive dysfunction and neuronal damage and have become a clinical challenge with modern- daylifestyle. Neuro-protective phyto-compound rich functional foods are in vogue in consideration with the rampant emergence of progressive neurodegenerative diseases worldwide. Several pre-clinical studies have unfolded the promising neuroprotective efficacy of *L. ruthenicum Murr* fruits and offered compelling evidences for biological activity. *Lycium ruthenicum Murr* anthocyanin extract has shown promise in an animal model of amyloid beta-protein 1–42 induced Alzheimer's disease. The extract at a dose of 80 mg/kg, could improve the animal's memory capacity in a passive-avoidance test in a shuttle box and significantly reduce markers of neuronal oxidative stress and inflammation in the hippocampus tissue of the rat brain [70, 89]. In the following years, Chen et al [69] re-validated and suggested an underlying biological mechanism for the protective benefits of *L. ruthenicum Murr* anthocyanins in



**134**



**135. R = OMe**
**136.. R = H**

**Fig. 7** Representative Structure of Coumarins and Cinamate derivatives

an animal model of d-galactose induced memory impairment. In their study, anthocyanins were shown to lower the Bax/Bcl-2 ratio, caspase-3, C-jun N-terminal kinase (p-JNK) levels with evident alleviation of memory dysfunction and neuroinflammation in an animal model.

Hypoxia is the hallmark of most neurodegenerative diseases. Preclinical evidence has been generated to show that black gojiberry extracts could protect the cortical neurons against conditions of oxygen-glucose deprivation/reperfusion. In a recent study, the specific activity of polysaccharide 3 (LRP3) of *L. ruthenicum Murr* was evaluated in an animal model of hypoxic-ischemic encephalopathy. LRP3 pre-treatment could induce expression of protective nuclear factor erythroid 2-related factor (Nrf2) and heme oxygenase-1 (HO-1). The specificity of protection was shown by reversal of protection by s-RNA based inhibition Nrf2/HO-1 pathway [90]. Based on existing knowledge, very recently a network of *L.ruthenicum Murr* chemicals, putative biological targets and major pathways of Alzheimer's disease has been produced. Interestingly, in this path-breaking study, 12 core genes have been identified which are potentially modulated by *Lycium ruthenicum Murr* extract and could be responsible for its potent activities [91]. Such studies are set to give most sought after answer to biological mechanisms behind the plethora of observed biological efficacies of black goji berries.

#### Gastrointestinal (GI) activity

In an in-vitro digestion stimulation study, anthocyanins from *L. ruthenicum Murr* have been reported to positively impact intestinal health both by encouraging the growth of health- promoting human gut microbiota as well as biosynthesis of short-chain fatty acids (SCFAs) during in-vitro fermentation [92]. It is reported earlier that gut microbiota participates in anthocyanin metabolism and absorption; in turn anthocyanin metabolites have pro-biotic activities for maintenance of healthy gut microbiota [93]. Anthocyanins significantly increased the relative abundances of *Bifidobacterium* and Allisonella, and reduced the relative abundances of *Prevotella, Dialister, Megamonas* and *Clostridium.* In proof of concept in-vivo study by Peng et al [94], prolonged treatment of mice with crude extract of anthocyanins from *L. ruthenicum Murr* fruits, showed its positive effect of strengthening intestinal barrier (via*.* Upregulation of barrier proteins Zo-1, Occludin, Claudin-1 and Muc1) and proliferation of gut microbiota (*Coprobacter*, *Barnesiella*, *Eisenbergiella, Alistipes*, and *Odoribacter*). This was a recapitulation and validation of findings by Luo et al [91] wherein C57BL/6 mice fed with *L. ruthenicum Murr* showed significant enrichment of fecal microbiota and SCFAs along with improved intestinal immune barrier functions, reduced permeability, free ammonia *etc* in comparison to the antibiotic treatment group.

#### Hypoglycemic effect

Very limited evidence of the hypoglycemic effect of *L. ruthenicum Murr* fruits is available in the scientific literature. In a study by Wang et al., the anti-hyperglycemic efficacy of polysaccharide extracts of *L. ruthenicum Murr* fruits was evaluated in alloxan- induced diabetes model in mice. In this study, 21 days of polysaccharide extract supplementation could downregulate hyperglycemia and restored conversion of blood glucose into liver glycogen reserves along with lowering of oxidative damage markers [95].

#### Antifatigue effect

The polysaccharides from medicinal plants have been reported as natural anti-fatigue substances by several researchers [54, 96–99]. Different doses of water-soluble polysaccharides from *L. ruthenicum Murr* (50, 100 and 200 mg/kg) have been tested for anti-fatigue activity in a rodent model of forced swim test (FST) [96]. The highest dose showed promising anti-fatigue activity based on standard fatigue markers such as lactic dehydrogenase, blood urea nitrogen, triglycerides, creatine phosphokinases etc. Plausible underlying mechanisms are proposed to be triglyceride mobilization for energy generation and upregulation of anti-oxidant activity markers such as GSH, GPx and SOD [19]. In a study of anti-fatigue and

**Table 10** Identified Anthocyanins of Black Goji Berry

| S.No | Name | Reference |
|---|---|---|
| 137. | Peonidin 3-O-[6-O-(4-O-E-p-coumaroyl-O-α-rhamnopyranosyl)-β-glucopyranoside]-5-O-β- glucopyranoside | [62] |
| 138. | Petunidin 3-O-[6-O-(4-O-trans-p-coumaroyl-O-α- rhamnopyranosyl)-β-glucopyranoside]-5-O-β- glucopyranoside | [3, 41] |
| 139. | Petunidin 3-O-[6-O-(4-O-(cis-p coumaroyl)-α-L- rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β- D-glucopyranoside] | [41, 42] |
| 140. | Petunidin 3-O-[6-O-(4-O-(trans-p-caffeoyl)-α-L- rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside] | [41, 42] |
| 141. | Petunidin 3-O-[6-O-(4-O-(4-O-trans-(β-D- glucopyranoside)-p-coumaroyl)-α-L rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β- D-glucopyranoside]. | [41, 42] |
| 142. | Petunidin 3-O-[6-O-(4-O-(4-O-cis-(β-D- glucopyranoside)-pcoumaroyl)-α-L- rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D-glucopyranoside]. | [41, 42] |
| 143. | Petunidin 3-trans-caffeoylrutinoside-5-glucoside | [67] |
| 144. | Petunidin-3-feruloylrutinoside-5-glucoside | [67] |
| 145. | Petunidin 3-cis-p-coumaroylrutinoside-5-glucoside | [25, 63, 68] |
| 146. | Petunidin 3-trans-p-coumaroylrutinoside-5-glucoside | [25, 42, 63, 67, 68] |
| 147. | Petunidin 3-rutinoside-5-glucoside | [67] |
| 148. | Petunidin 3-O-rutinoside (glucosyl-cis-p-coumaroyl)-5-O- glucoside | [25, 68] |
| 149. | Petunidin 3-O-rutinoside (glucosyl-trans-p-coumaroyl)-5-O- glucoside | [25, 68] |
| 150. | Pentuidin-3-O-(caffeoyl)-rutinoside-5-O-glucoside | [66] |
| 151 | Petunidin-3-O-(glucosyl-p-coumaroyl)-rutinoside-5-O-glucoside | [66] |
| 152 | petunidin-3-O-(p coumaroyl)-rutinoside-5-O-glucoside | [66] |
| 153. | Delphinidin 3-glucosyl-trans-p-coumaroylrutinoside-5-glucoside | [42] |
| 154. | delphinidin 3-O-[6-O-(4-O-p-coumaroyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside]-5-O-[β-D- glucopyranoside] | [69] |
| 155. | Delphinidin 3-cis-p-coumaroylrutinoside-5-glucoside | [25, 42, 63, 68] |
| 156 | Delphinidin 3-trans-p-coumaroylrutinoside-5-glucoside | [25, 42, 63, 68] |
| 157 | Malvidin-3-glucosyl-cis-p-coumaroylrutinoside-5-O-glucoside | [42] |
| 158 | Malvidin-3-glucosyl-trans-p-coumaroylrutinoside-5-O-glucoside | [42] |
| 159. | Malvidin-3-O-(p-coumaroyl)-rutinoside-5-O-glucoside | [66] |
| 160. | Malvidin-3-rutinoside-(feruloyl)-5-O-glucoside | [25, 42] |
| 161. | Malvidin-3-O-rutinoside-5-O-glucoside | [42] |
| 162. | Malvidin-3-cis-p-coumaroylrutinoside-5-O-glucoside | [25, 42, 63, 68] |
| 163. | Malvidin-3-trans-p-coumaroylrutinoside-5-O-glucoside | [42, 67] |
| 164 | Cyanidin-3-O-glucoside | [25, 67] |
| 165 | Cyanidin-3-O-galactoside | [25] |
| 166 | Cyanidin-3, 5-O-diglucoside | [25] |
| 167. | Cyanidin-3-O-rutinoside | [66] |
| 168 | Pelargonidin − 3-O-glucoside | [25, 33] |
| 169. | Pelargonidin − 3-O-galactoside | [25] |
| 170. | Pelargonidin-3-O-diglucoside | [25] |
| 171. | Petunidin-3, 5-O-diglucosides | [25] |
| 172. | petunidin-3-glucoside | [33] |
| 173 | Petundin-3-O-glucoside-5-O-glucoside | [25, 63, 68] |
| 174 | Petundin-3-O-galactoside-5-O-glucoside | [25, 63, 68] |
| 175 | Pentunidin-3-O-glucoside-(feruloyl)-5-O- glucoside | [25, 68] |
| 176. | Pentunidin-3-O-glucoside-(maloyl)-5-O-glucoside | [25, 68] |
| 177. | malvidin-3-glucoside | [33] |
| 178. | peonidin-3-glucoside | [33] |
| 179 | Delphinidin-3-glucoside | [33] |

**Table 10** Identified Anthocyanins of Black Goji Berry *(Continued)*

| S.No | Name | Reference |
|---|---|---|
| 180 | Delphinidin – 3-O-(6′-p-coumaryl)-Glucoside | [25] |
| 181. | Malvidin | [33] |
| 182. | Cyanidin | [33] |
| 183. | Petunidin | [33] |
| 184. | Pelargonidin | [33] |
| 185 | Peonidin | [33] |

myocardial protection by *L. ruthenicum* extract (extracts 0.10, 0.1, 0.15 g/mL, drug dose 0.1 ml/10 g), American Ginseng powder (0.05 g/mL) was used as a positive control. *L. ruthenicum Murr* extract could extend the weight loaded swimming time, decreased blood lactic acid and urea nitrogen levels along with enhanced muscle and liver glycogen reservoirs [67]. Improved anti-fatigue effect of microcapsules loading of *L. ruthenicum Murr* anthocyanidins by modified b-glucan from highland barley has also been shown [100]. Some experimental results demonstrate that *L. ruthenicum Murr* can increase blood sugar, reduce lactic acid content and increase glycogen reserve in mice, which has good alleviating resistance to exercise-induced fatigue [32].

## Radioprotective effects

In a mice model of radiation- induced injury, *L. ruthenicum Murr* extract (dose 2 g/kg and 4 g/kg) shows a reduction in caspase-3 and caspase-6 expression following 5Gy irradiation. This was also associated with a significant increase in total red blood cells, DNA and hemoglobin content in comparison with the standard drug control group amifostine (WR-27212015) [101].

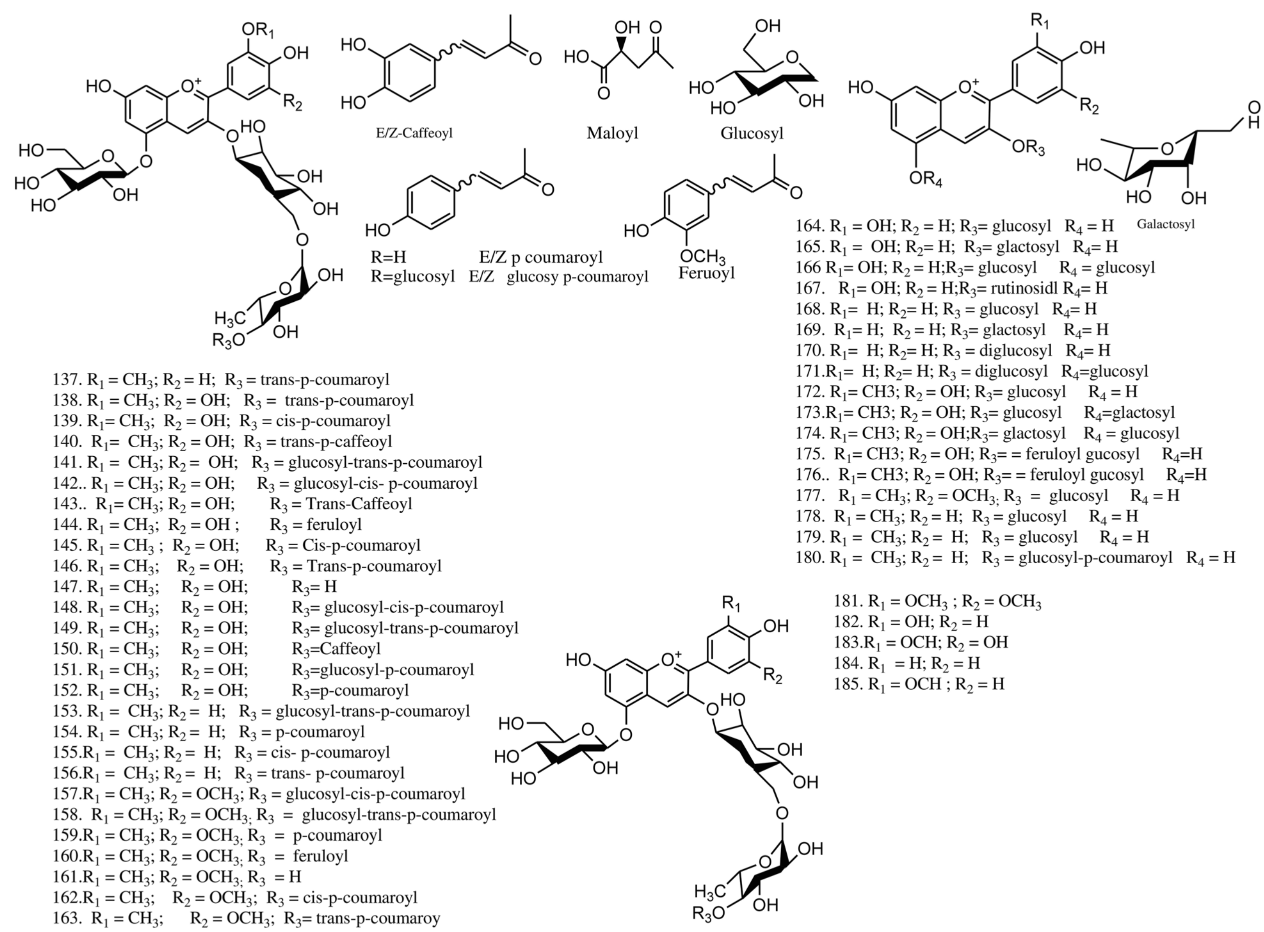



**Fig. 8** Representative Structure of Anthocyanins

## Immuno-modulatory effects

The pectin content of *L. ruthenicum Murr* has been proposed to be responsible for its observed immunomodulatory efficacy. In an in-vitro study, Peng et al. [37] have shown immunomodulatory functions of isolated pectin from *L. ruthenicum Murr* in mouse macrophage RAW264.7 cell line. The results indicated that treatment with pectin stimulated the macrophages to produce a higher level of NO which is the mediator in the regulation of immunological functions. In an in-vivo evaluation, the efficacy of its polysaccharide preparation (LRGP3) has been tested in a mouse model of cyclophosphamide-induced immunosuppression [102]. Administration of all the doses (25, 50 and 100 mg/kg) for 10 days boosted recovery of indices in thymus and spleen, B and T cell proliferation, phagocytic activities of peritoneal macrophages, restoration of cytokine profile.

## Hepatoprotective effects

Treatment of high-fat-diet fed C57/BL mice with *L. ruthenicum Murr* fruit extract (2 g/kg and 5 g/kg doses) has been shown to have hepatoprotective effects by regulation of AMPK signaling pathway. *L. ruthenicum Murr* extract supplementation could downregulate fatty acid synthase and sterol regulatory element-binding protein 1c along with upregulation of peroxisome proliferator -activated receptor α and peroxisome proliferator activated receptor γ coactivator 1α. This also co-existed with significantly reduced triglycerides, total cholesterol, aspartate aminotransferase and alanine aminotransferase in the serum, improved glucose metabolism and insulin sensitivity in NAFLD mice [103].

## Toxicology and adverse reactions

Like most other commonly consumed wild fruits, *L. ruthenicum Murr* is also proposed to be non-toxic and has been used traditionally as food as well as herbal medicine without any observed or reported toxicity. A Chinese study, about the toxicological investigations on this plant has concluded *L. ruthenicum Murr* fruit as non-toxic. In this study, acute toxicity test, Ames test, bone marrow cell micronucleus, sperm shape abnormality test, thirty days feeding test were conducted. The MTD of *L. ruthenicum Murr* pigment growth in mice and rats was found greater than 30,000 mg/(kg.bw) and thus claimed safe for consumption. Also, the mutagenic test was found negative and no abnormal phenomenon was observed in rats after being fed for 90 days. Interestingly, anthocyanin enriched herbal extracts of black gojiberries showed activity for the treatment of chronic myeloid leukemia (CML) [104]. Biological activity tests showed that LRP3-S1 could inhibit the growth of pancreatic cancer cells. Also, LRP3-S1 could attenuate the invasion ability of BxPC-3 cells and downregulate protein expression of p-FAK, p-AKT, p-GSK-3β and p-p38 MAP kinase [33].

## Natural colorant

In recent years, the use of natural pigments has remarkably increased in the food color industry due to growing awareness of the environmental hazards and the potential side effects of the synthetic chemicals being used as food colorants. Thus, many researchers are exploring the potentials of black goji berries to be used as a natural food grade blue color across wide range of pH conditions. Petunidin-3-trans-p-coumaroyl-rutinoside-5-glucoside is proposed to be the biggest contributor in color of black gojiberry [105, 106].

## Future perspective

Phytochemical studies of *L. ruthenicum Murr* have revealed the presence of more than a hundred compounds. The crude extracts and some of the purified constituents of the black goji berry are reported to possess plethora of biological activities as well. Chiefly, the significantly higher content of anthocyanins, polysaccharides, spermine and spermidine alkaloids are accounted for most of these biological activities. Black goji berry has been used in the traditional medicinal system without any reported toxicity. The altitudes at which this plant is known to grow wildly, acute mountain sickness (AMS) is a predominant health concern to the sojourners that can further lead to potentially life threatening altitude illnesses such as High Altitude Cerebral Oedema (HACE) and High Altitude Pulmonary Oedema (HAPE). Oxidative stress, inflammatory stress and nitrosative stress are the main underlying causes behind high altitude sickness. Since black goji berry possess strong anti inflammatory, anti-fatigue and antioxidant activities, it deserves to be explored for its utility for development of a range of pharmaceuticals, cosmetics, food additives and nutraceutical products for curing diseases and general maintenance of well being at high altitude. Additionally, owing to its enriched content of photo-stable and thermo-stable anthocyanins, the plant has tremendous applications as natural food colorant. There are ample research opportunities to explore the phyto-chemistry, biological activities and safety for development of quality products from *Lycium ruthenicum Murr* with wide applications (Fig. 9). Hence, from the above mentioned reports it can be concluded that *L. ruthenicum Murr* has immense potential to cure various diseases and this less explored but high value medicinal plant of Indian Trans-Himalaya, particularly Ladakh has enormous importance in traditional system of medicine (Amchi System of Medicine). Although a lot of exploration has been done, still there is a need of in-depth scientific validation of its biological activities and underlying biological mechanisms for bio-active components of this plant for development of herbal preparations/ products.

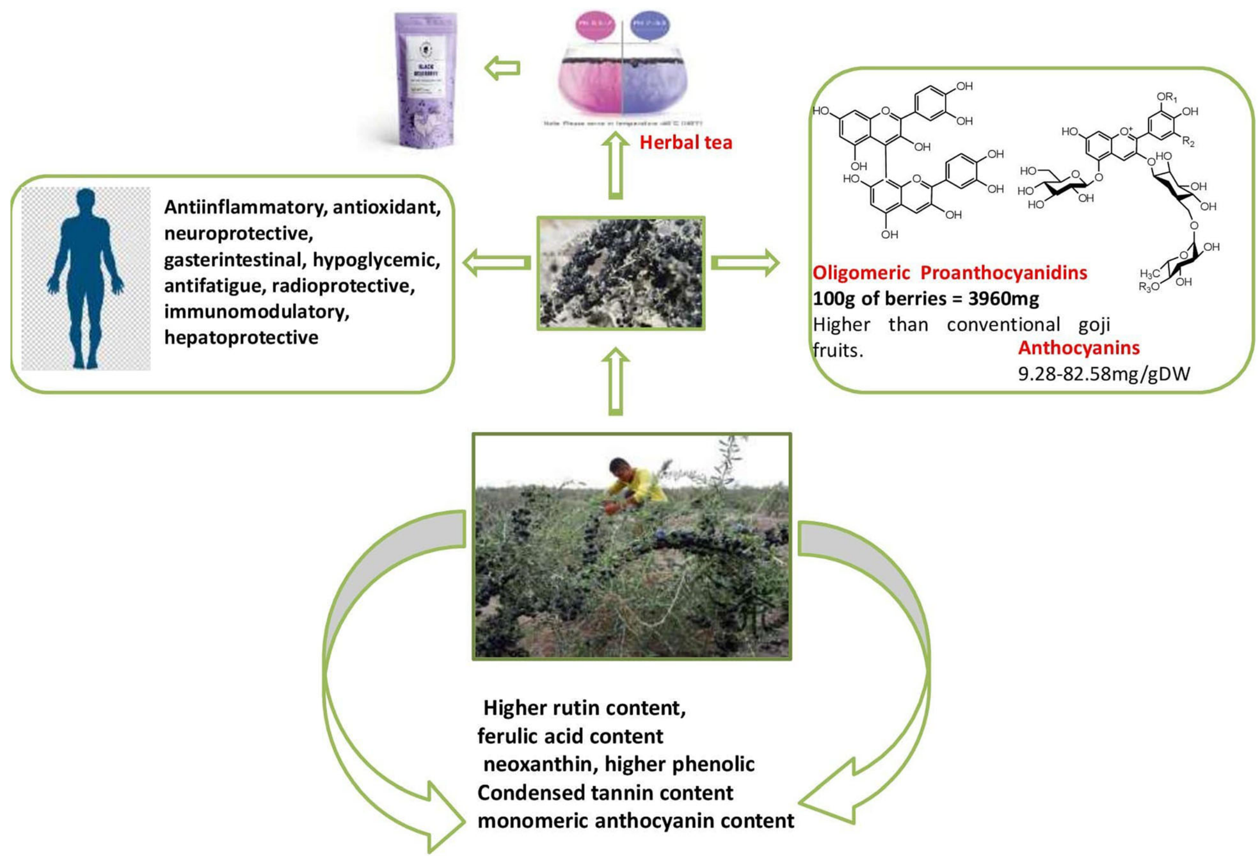



**Fig. 9** Phytochemical and Pharmacological evidence of *Lycium ruthenicum*

## Conclusions

We have critically reviewed the bioactive components and their biological activities from *L.ruthenicum Murr* with their respective structures. A unique color of anthocyanins reported from black goji berries possesses most of the pharmacological activities which makes *L.ruthenicum Murr*, a good candidate for exploration of therapeutic properties.

### Abbreviations

ABTS: 2,2′-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid; DW: Dry weight; Dhc: Dihydrocaffeoyl; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FW: Fresh weight; FRAP: Ferric reducing/antioxidant power; GAE: Gallic Acid Equivalent; iNOS: inducible nitric oxide synthase; IL: Interleukin; NF-kB: Nuclear factor κB; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TPC: Total phenolic content; TFC: Total flavonoid content; TE: Tanin equivalent; TNF-α: Tumor necrosis factor-α; VE: Vitamin E

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We would like to dedicate this article to the ethnic communities who perfected and preserved the traditional knowledge about health promoting properties of the genus lycium.

### Authors' contributions

All authors contributed equally to literature research, writing manuscript etc. The author(s) read and approved the final manuscript.

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### Availability of data and materials

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## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

The authors consent for the publication of this review.

### Competing interests

The authors declare that they have no potential conflicts of interest.

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