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SHORT REVIEW

Ethnopharmacology of Genus *Rubus*: Modern Science from Ancient Science

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Abstract

From the prehistoric, ancient age to the modern-day, genus *Rubus* species are already known for their healing properties such as in neurodegenerative and psychological disorders, cancer, diarrhoea, colic pain, diabetes, nephrological, and inflammatory disorders. Based on their phytochemistry and pharmacology it is an attempt to achieve a greater knowledge of the biological significance of these herbal medicinal plants. The ultimate aim of this review is to deliver the magnification of research at the cellular and molecular level in the management of nervous breakdowns and other diseases. An exhaustive literature search was performed by online databases such as Springer, Scopus, and Elsevier. In this review, the different novel medicinal plants belong to the genus *Rubus*, used to treat enormous ailments based on traditional and literature search, their potential bioactive species belong to the same genus.

Keywords: Ethnomedicine, Pharmacological Properties, Phytochemistry, *Rubus*, Traditional Uses, Translational Value

1. Introduction

The use of herbal remedies is becoming more and more common worldwide. It is estimated that at some point in their lives, about 80% of the Indian population use a traditional remedy. Traditional remedies are part of India's cultural and religious life. In addition, its accessibility and affordability are due to the wide use of traditional medicine. India has a large number of tribes, which is reflected in the medical systems practiced[1]. This treasure of knowledge has historically been transmitted orally, from one generation to another without any written records[2] and various indigenous communities around the world still maintain it. Documenting indigenous information through ethnobotanical studies is an essential use for conserving biological resources.

Asia is the source of among the most medicinal plant since ancient times one of the well-recognized Genera is *Rubus* which includes more than 750 species in 12 subgenera, the geographical location indicates that it presents all continents except Antarctica[3]. *Rubus* species have been used in folk medicine because it possesses the ethnomedicinal property and it was always been the subject of research over the last twenty-five years has been performed on *Rubus* species, a number of the study have been performed including the ability

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to modulate neuroinflammation[4], glucoregulation[5], neurodegeneration[6] and hippocampal neurogenesis[7]. These all effects resembled their phytoconstituents present in *Rubus*. The *Rubus* species are commonly recognized as shrubs (including blackberries and raspberries), thus which are widely disseminated from North Temperate Zone to the tropics (Southern Hemisphere) throughout the globe[8].

2. Phytochemistry

To date, more than 350 species are known for their pharmacotherapeutics activities which belong to the genus *Rubus* and have been chemically investigated, isolated, and characterizing the active bioactive constituents present therein. *Rubus* species are rich in pharmacologically important constituents that have been documented in recent years, i.e., flavonoids, polyphenols, anthocyanins and triterpenoids. A list of the phytoconstituents of *Rubus* species compiled from various sources is given below.

2.1 Phenolic Compounds

In *Rubus* species, hydrolysable tannins represent the primary class of phenolic compounds (gallo and ellagitannins), anthocyanins are the second most bioactive element are other minors are flavonols, flavan-3-ols, hydroxycinnamic acids, and proanthocyanidins. Certain phenolic groups of medicinal properties have been found in the *Rubus*. Some bioactive constituents have been reported such as tannins; a core polyolyol tannin consists of hydrolysable tannins (e.g., quinic acid/glucose), and the most widely identified tannins in the genus *Rubus* is ellagitannins[9]. Various intermediate inflammatory agents, including the Inductive Nitric Oxide Synthase (INOS), Nuclear Factor kappa-β (NF-kβ), Tumor Necrosis Factor-alpha (TNF-α), Cyclooxygenase-2 (COX-2) and Interleukin-6 (IL-6) have been reported to attenuate polyphenols, such as ellagic acid[10].

2.2 Flavonoids

Flavonoids are a complex group of polyphenolic plant metabolites found in human feed. Kaempferol and quercetin glycosides are the key components extracted from *Rubus* plants such as rutin etc. (all details mentioned in Table 1). The target versatility of flavonoids allows them to activate various mechanisms within the CNS, including certain enzymatic inhibition, receptor/transporter modulation, neurotransmission via serotonergic and noradrenergic systems[11].

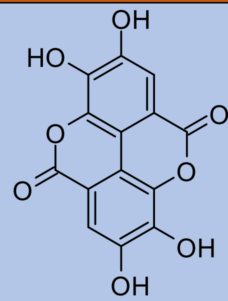
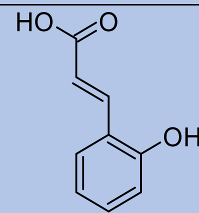
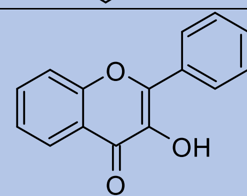
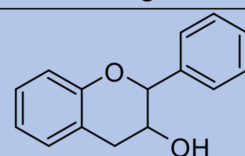
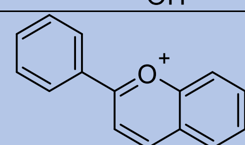
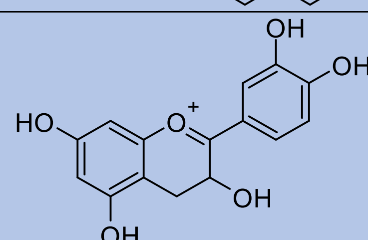
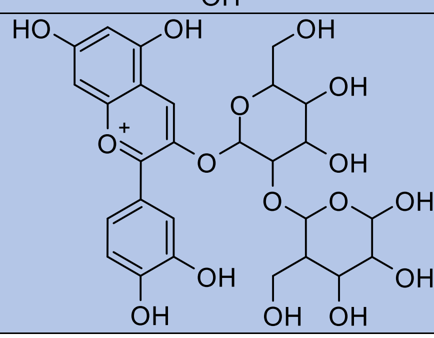
2.3 Anthocyanins

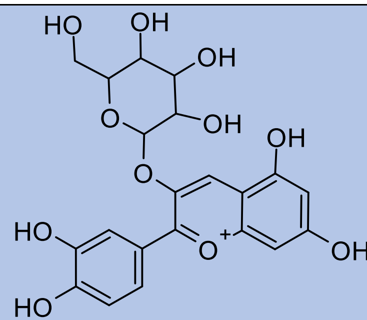
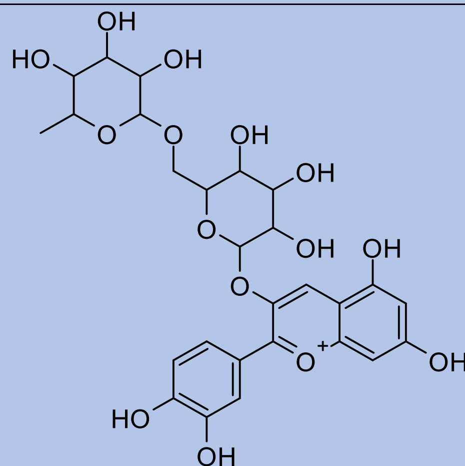
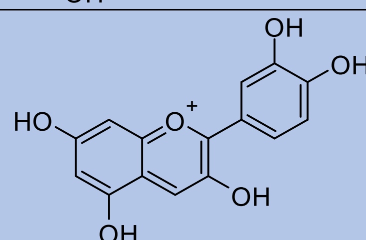
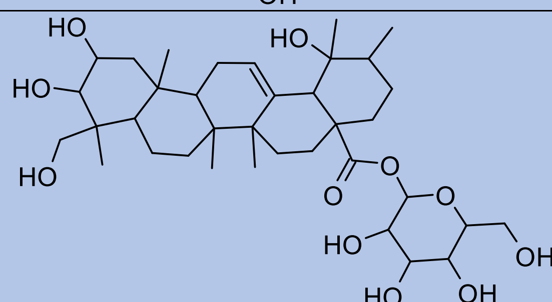
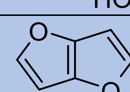
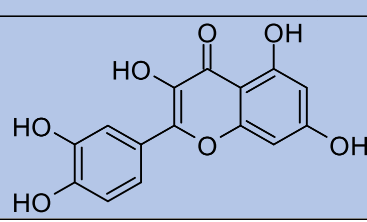
Anthocyanins are a group of phenolic compounds that occur naturally, charged with the color of many plants, vegetables and flowers[12]. The primary constituent is cyanidine, cyanidine-3-sophoroside, with smaller quantities of other anthocyanins including cyanidine-3-(2G-glucosylrutinoside), cyanidine-3-glucoside, cyanidine-3-rutinoside and pelargonidine and its glycosides. Anthocyanin has been shown to play a significant role in the ability to scavenge free radicals, triggering and controlling genes responsible for xenobiotic metabolism, altering cellular signals, and apoptosis[13]. Anthocyanins which are the main phytoconstituent of *Rubus* can have therapeutic potential against oxidative stress induced by age-related neuronal deficits[14].

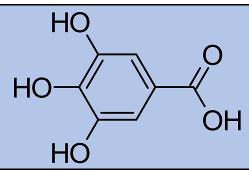
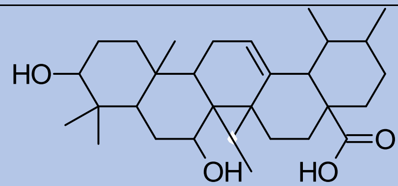
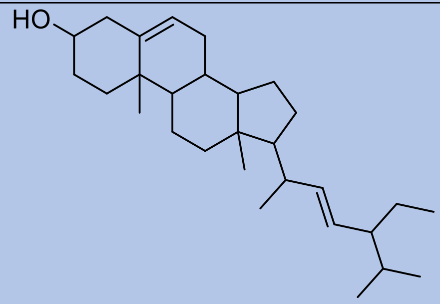
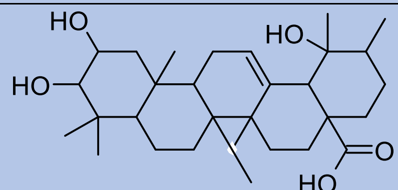
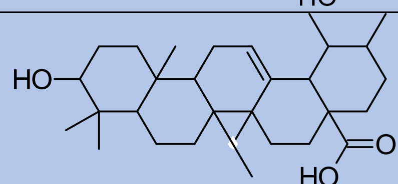
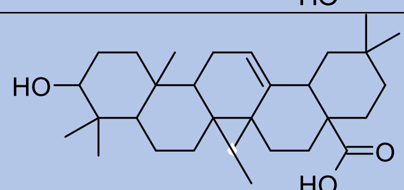
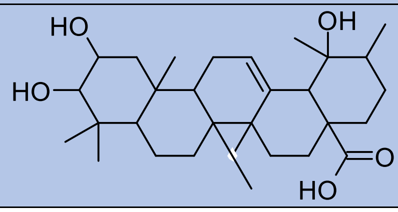
2.4 Terpenoids and Steroids

In the plant world, terpenoids exist in abundance, where they have several different roles; triterpenoids are the most common terpenoids found in the *Rubus* genus, the characteristic triterpenic constituents of *Rubus* species, are triterpenes of the ursane type, chemically, nigaichigoside F1 is known as 28-O-glucoside 23-hydroxytormentic acid and aglycone 23-hydroxytormentic acid is labelled as triterpenoids 19α-hydroxyursanetype (listed in Table 1).

Table 1. Chemical constituents and their chemical structures present in genus *Rubus*

S.No	Phytoconstituent	Chemical Structure
1.	Ellagitannins	
2.	Hydroxycinnamic acids	
3.	Flavonols	
4.	Flavan-3-ols	
5.	Anthocyanins	
6.	Cyanidine	
7.	Cyanidine-3-sophoroside	

8.	Cyanidine-3-glucoside	
9.	Cyanidine-3-rutinoside	
10.	Pelargonidine	
11.	Nigaichigoside F1	
12.	Furofuran	
13.	Quercetin	

14.	Gallic acid	
15.	Rubitic acid	
16.	Stigmasterol	
17.	Euscaphic acid	
18.	Ursolic acid	
19.	Oleanolic acid	
20.	Tormentic acid	

3. Traditional Uses of *Rubus* Species

For various reasons, folk knowledge transmitted without any formal mechanism regarding the uses of medicinal plants and the conventional healing approach may not be of interest to younger generations. Thus, such information is likely to risk disappearing in the future. Therefore, this report seeks to explain the geographical reality of the widespread use of medicinal plants and offers valuable knowledge about the key species used in communities. From a scientific perspective, establishing a logical relationship is necessary between the chemical, biological and therapeutic activities of folk medicine in areas where *Rubus* is located; knowledge of the past is mixed with newly integrated information highlighting the cultural changes that this region is experiencing. *Rubus* is a perennial shrub that is most significant for Indian therapy including bacterial infections, anxiety, pain and inflammation, wounds, ulcers, abortion, diabetes, gastrointestinal disorders and astringent bacterial/fungal infections[15], carminative, the diuretic action of the leaves and the bark[16], febrifuge, kidney, miscellany, stomachic properties. *Rubus* leaves are alleged to be flavoured to assist with digestive disorders, childbirth, and menopause. For ages, young *Rubus* species shoots have been used in folk medicine for the treatment of wounds, infected insect bites and pimples[17]. Genus *Rubus* was commonly used for symptoms associated with nervous disorders such as spasmolytic, antidepressant analgesics and sedatives. In the treatment of fever, colic, cough and sore throat, fruit juice is used, the inner bark is used in Tibetan medicine, it is said to have a sweet and acidic flavour and heating capacity[18]. It is also used in the treatment of sensory loss, vaginal/seminal discharge, polyuria and sleep micturition[19]. The entire part of the plant is a blessing for various diseases to be treated therapeutically.

3.1 Pharmacological Activities

The main focus of pharmacological research was on the bioactivity of different isolated compounds in fractions from plant species of the genus *Rubus*.

3.1.1 Anti-Inflammatory Activity

Flavonoids (quercetin, hyperoside, tiliroside, astragalin and 3-rutinoside kaempferol) and other important substances are the key phytoconstituents responsible for anti-inflammatory activity[20], the medicinal plant belongs to the *Rubus* genus have possessed anti-inflammatory activity listed in Table 1.

3.1.2 Nephroprotective Function

Genus *Rubus*, traditionally used in the management of the kidney-related disorder, renal tonic, diuretic, is used as shown by *in vivo* research in the treatment of sensory impairment, vaginal/seminal discharge, polyuria and sleep-related micturation. The development of phytoconstituents of alkaloids, saponins, tannins, triterpenoids and flavonoids in the plant indicates nephroprotective behaviour[19].

3.1.3 Antioxidant

Phenolic compounds were shown to have a significant ability to scavenge radical oxygen species and prevent oxidation and pathogenic growth of bacteria. Considerable compounds present throughout edible plants and herbs including such flavonoids, phenolic acids, catechins, lignans have antioxidant properties[21]. For example, reduced risk of cardiovascular, cancer and neurological disorder has been positively correlated with dietary antioxidant intake. Natural antioxidants have become progressively an important field of study[22]. And researchers and scientists prove that the genus *Rubus* is recognised to have promising antioxidant properties that play a crucial part in the treatment of different ailments (Table 1).

3.1.4 Hypolipidemic Activity

Several studies have shown that raspberry leaf treatment has an important hypolipidemic effect, indicated by reduced total serum cholesterol and triacylglycerol levels. It was also proposed that raspberry leaves could be further explored as a drug for the treatment of hyperlipidaemia diseases. It has been found that ellagitannin-rich extracts inhibit LDL cholesterol oxidation and reduce its aggregation in macrophages[23]. Ellagitannins have a beneficial impact on blood vessel function by inducing nitric oxide synthase production in the endothelium of the circulatory system. Ellagitannins inhibit platelet aggregation processes and monocyte and endothelial cell adhesion. Metabolites of ellagitannin display anti-atherosclerotic properties. Ellagic acid also inhibits the expression of the factor VCAM-1, which in the early stages of atherosclerosis, plays a key role.

3.1.5 Antihypotensive Activity

In the management of anti-hypotensive behaviour, the genus *Rubus* has historically been reported. Through a sympatholytic or parasympathomimetic phase, there is a chance that the extract may induce its hypotensive impact. The genus *Rubus* can decrease blood pressure by interfering with the sympathetic nervous system inhibition, which reduces arterial pressure due to the possible phytoconstituent present in it[24] or due to the cholinergic neurotransmitter's inhibitory effects, acetylcholine and parasympathetic stimulation results in hypotension on smooth cardiac and vascular muscle[25]. It was demonstrated in a review that the extract of ethanol through stimulation of the guanylate cyclase/cGMP/NO/cGMP pathway and the Akt-eNOS pathway[26].

3.1.6 Anti-aging Activity

Due to their rich content of polyphenols, saponins, terpenoids, polyphenols and flavonoids, *Rubus* genus is ethnomedicinally used for anti-aging activity. A new glycoprotein that has been isolated from *R. chingii*, D-galactose-induced aging mice model improved expression of the klotho anti-aging gene and restored renal function were shown to have major anti-aging effects[27].

3.1.7 Anti-microbial Activity

The anti-microbial activity of the genus *Rubus* has been extensively studied. *Rubus chingii, Rubus elliptical, Rubus corchorifolia, Rubus chamaemorus, Rubus parvifolius, Rubus racemosus, Rubus setchuenensis* a mild antibacterial effect is for flavonoids showed against minimal inhibitory concentrations of *Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Penicillium*[28].

3.1.8 Antineoplastic Activity

Polyphenolic compounds (quercetin, kaempferol, and ellagitannins present in *Rubus* plant material) illustrate anti-proliferative effects[28]. This phytoconstituents express reductive action on free radicals and can limit mutations or even engage in DNA repair[29]. The latest findings have shown that the genus *Rubus* possesses a possible resistance to chemo-preventive cancer. Research shows anticancer properties of *Rubus coreanus, Rubus fairholmianus, Rubus idaeus, Rubus chingii, Rubus corchorifolius, Rubus caesius, Rubus ellipticus* and other *Rubus* species to significantly reduce cancer cell growth and function as an effective anti-proliferative activity (Table 1).

3.1.9 Anti-infectious Activity

Different mechanisms and synergistic or additive effects are suggested to be responsible for their antibacterial activity between organic acids, (citric, benzoic, malic, etc.) phenolic acids, tannins and other components of the berry extracts. Hydrophobicity of the materials-polymeric phenolics or organic acids helps them to stack and accumulate in the membrane of the microbial cell[30]. *Rubus* is effective against *Salmonella typhimurium, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, Streptococcus faecalis, Bacillus cereus, Staphylococcus saprophyticus, Listeria monocytogenes* and *Lactobacillus strains.*

3.1.10 Contribution of Rubus species in Cancer

High concentrations of ellagic acid were found in the fruits of the genus *Rubus* in the family *Rosaceae*. Ellagic acid has an anti-carcinogenic, broad-spectron effect. The compound was found to inhibit tumor DNA polymerases as well as carcinogens in investigations carried out in animal models, e.g., Benzo(a)pyrene, 3-methylcholanthrene, N-2-flurenylacetamide, aflatoxin B1. This acid reacted with an inactive complex of free radicals and with the carcinogenic epoxide benzo(a)pyrene diol, resulting in the formation of a new compound without carcinogenic properties and with an open epoxide pyrene ring. Ellagic acid has an anti-carcinogenic effect on the factor VEGF-A, which is involved in endothelial cell formation, proliferation and migration in bladder cancer[31]. By inhibiting the proliferation of tumour cells, triggering their apoptosis, influencing inflammatory processes and disrupting angiogenesis processes, the compound prevents metastasis and the growth of different cancer types. The key phytoconstituents present in the genus *Rubus* (sanguin H-6 and lambertianin C) are ellagitannins, which exert an anti-proliferative effect on the cell line of cervical cancer[32,33]. In leukaemia cell line (HL-60) studies, cytotoxic activity of sanguiin H-6 was shown as recorded regular intake of ellagitannins and ellagic acid induces apoptosis of cancer cells via an effect on mitochondria.

In a series of cancer cell lines, gallic acid displayed a major inhibition of cell proliferation and driven apoptosis in cells of esophageal cancer (TE-2) but not in cells of non-cancer (CHEK-1). The apoptosis molecular mechanism showed that gallic acid up-regulated the protein pro-apoptosis, Bax, and induced caspase-cascade activity in cancer cells. But on the other side, anti-apoptosis proteins like Bcl-2 and Xiap have been down-regulated by gallic acid. Furthermore, gallic acid also altered down-regulation of the Akt/mTOR survival pathway[33]. Scientists have analysed slow down expression of proteins linked to pro-apoptosis in non-cancerous cells. The findings indicate that gallic acid may be a possible compound for cancer[34].

4. Conclusion

In this review the therapeutic potential, phytochemistry, pharmacological and traditional aspects of the medicinal plants which belong to the genus *Rubus*, reported to possesses medicinal activities for the management of disorders such as endocrinological, digestive system, cardiovascular, inflammatory disorders were collected. As per this study, genus *Rubus* show various pharmacological activities such as anti-oxidant, anti-aging, anti-neoplastic, anti-microbial, anti-infectious, hypolipidemic, anti-hypotensive activity.

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6. Authors' Contributions

All the authors contributed equally to the works presented in paper.

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