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Phytochemistry and Therapeutic Potential of *Acacia ferruginea*: A Systematic Review

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ABSTRACT

Background: *Medicinal plants have a proven and promising role in the cure of various diseases. The aim of this mini review is to document the therapeutic effect and phytochemical prospects of one of the traditionally important Acacia plant species called Acacia ferruginea.*

Methods: *Information on Acacia ferruginea was collected from various electronic databases like Google Scholar, PubMed, Web of Science, Science Direct, Scopus.*

Result: *The presence of flavonoids, alkaloids, phenolics, tannins, saponins has been ascertined by qualitative and quantitative analysis. The antioxidant, anti-cancer, anti-diabetic, anti-bacterial, anti-fungal, anti-haemorrhoidal, larvicidal activities of the plant have been documented. It is found that the bark of the plant is much investigated.0*

Discussion and Conclusion: *Documentation of Acacia ferruginea is needed due its potential in healing tropical diseases. The authors emphasize the need for future in-depth research to investigate the pharmacological activity, safety and clinical efficacy. Very limited information on this plant is available in the literature and validation regarding its chemical constituents is also needed to standardize its extracts and to evaluate its clinical applications.*

Key words: *Acacia ferruginea; Medicinal plants; Diabetes; Anti-cancer; Antioxidant*

Introduction

Plants are used all over the world for their medicinal benefits as they are a potential source of many therapeutic molecules. Since the Vedic period, medicinal plants have been used to eradicate and treat various causes of disease and epidemics. About every part of the plant have its own medicinal values. In our traditional systems of medicine Acacia species are widely used to treat various diseases like itching, leukoderma, ulcers, stomatitis and diseases of the blood. The generic name 'acacia' comes from the Greek word 'akis', meaning point. *Acacia ferruginea* is normally a small, drought-resistant, deciduous tree. Twigs are zigzag at nodes with green or reddish colour. Leaves are alternate and flowers are pale yellow, and pods contain a dark brown sweetish pulp. Seeds are flat ovate with greenish to brown colour. In India, flowers appear from March to May when the tree foliage is very scanty and pods ripen from November to February [1,2]. Several plants of Acacia species were claimed to possess traditional medicinal activities. One such Acacia species *Acacia ferruginea* belongs to *Mimosiaceae* family and has been reported to possess various pharmacological actions [3,4]. There are several records that plants of the *Acacia* genus have been commonly used in folk medicine for the management of pain, inflammation, cancer cure, hemorrhage, irritable bowel syndrome and leprosy [5,6]. The leaves are used to avoid bad breath and for curing liver complaints and dysentery; the bark possess strong antioxidant properties [7,8]. *A. ferruginea,* as a Nitrogen Fixing Tree (NFT) maintained, higher soil moisture status during all the growth stages on intercropped rainfed sorghum and significantly reduced nitrogen uptakes of stems, leaves and grain of cowpea and low fertility soils (alfisols) crops can be combined with NFT species like

A.ferruginea [9,10]. A comprehensive review aimed to provide a glimpse of the phytochemical profile and therapeutic applications of *A. ferruginea* is presented in this article.

Methods

The purpose of this study is to systematically analyse the medicinal properties and biological activities and therapeutic potential of *A. ferruginea*. The review includes studies conducted on the antioxidant, anti-cancer, anti-diabetic, anti-bacterial, anti-fungal, anti-haemorrhoidal, larvicidal activities of the plant and have been documented upto September 2020. Information on *Acacia ferruginea* was collected from various electronic databases like Google Scholar, PubMed, Web of Science, Science Direct, Scifinder and articles published in English language were included in this review.

Phytochemicals

Various forms of secondary metabolites present in medicinal plants plays an essential role in many diseases and are also used in the manufacture of medicines. A large number of plants have been reported to have different activities, such as antioxidant, anti-inflammatory, anti-parasitic, antibiotic, anti-hemolytic properties, etc. [11].

Alkaloids, flavonoids, saponins, tannins, triterpenoids, phenolic compounds, gums, mucilages, carbohydrates, proteins, amino acids are reported to be present in *A. ferruginea* [12]. Aerial parts tested positive to alkaloids, flavonoids, saponins, anthraquinones, tannins, glycosides, triterpenoids and phenolic compounds [13].

Quantitative analysis

Devi et al. reported that the total phenolics and tannins were found to be higher in 50% DMSO extract of leaves (14.8, 13.9%) than acetone extract (70%) of bark (4.6%, 3.7%) [14]. Methanol extract of *A. ferruginea* showed higher phenolic content (mg/GAE/100 µL) than aqueous extract (165.2 ± 6.0, 445.4 ± 8.6%) whereas pods showed 14.4% [15,16]. Pressure cooked *A. ferruginea* seed extracts showed decreased total phenolics and tannin content than raw seed extracts and enhanced iron chelating effect [17].

Chemical components (GC-MS/LC-MS)

Sowndhararajan et al. reported the presence of 12 components including catechin, procyanidin B1, quercetin, ellagic acid, rosmanol from GC/MS and LC/MS analysis of acetone extracts of *A. ferruginea* bark [18]. Derivatives of quinone (37.3%), quinoline (22.9%), imidazolidine (6.4%), pyrrolidine (4.5%) and cyclopentenone (3.5%) were identified as major components. Hexadecanoic acid, propanoic acid, pyridine, pyrazole and pyrimidine derivatives were also identified in the methanolic extract of *Acacia ferruginea* aerial parts. From the LC/MS analysis, derivatives of carboxamidine, imidazole, thiazole, catechin, coumarin were observed [13].

Biological Activities

Antioxidant activity

In the human body, certain diseases are caused by the overproduction of oxidants (reactive nitrogen and oxygen species) and to decrease the oxidative stress, scavenging of these oxidants is an effective way. It's been suggested that the illnesses caused by oxidative stress such as cardiovascular sicknesses, anticancer, anti-ageing diabetes mellitus, neurodegenerative illnesses and weight problems can be prevented by antioxidant phytochemicals. Consumption of fruits, medicinal plants, veggies reduces the risk of many chronic illnesses as they contain tremendous amount of antioxidant phytochemicals [19]. Sowndhararajan et al. recommended *Acacia ferruginea* bark in health supplements and functional foods due to higher antioxidants and nutraceutical content due to higher contents of total phenolics (11.70 g RE/100 g) [4]. Flavonoids in acetone extracts of *Acacia ferruginea* bark exhibited better activity than positive controls like Butylated Hydroxy Anisole (BHA) and α-tocopherol. Antioxidant assays of *Acacia ferruginea* bark (DPPH•, ABTS•+, and OH•, FRAP, metal chelation, phosphomolybdenum reduction and peroxidation inhibition) showed favourable results. Inhibitory activity of polyherbal extract containing *A. ferruginea* was recorded as 20.06 mcg/ml concentration [17]. Thippeswamy et al. concluded that, the antioxidant activity of *A. ferruginea* explains its widespread use in different herbal preparations to treat distinct pathogenic microbes and oxidative stress disorders since, DPPH scavenging activity (1000 µL), H_2O_2 reducing power, β-carotene linoleic acid assay of methanol extract of *A. ferruginea* was found to be higher [15]. *A. ferruginea* seeds exhibited higher hydrogen-donating ability than the positive standards such as ascorbic acid (30.12 mg), tannic acid (5.22 mg), pyrogallol

(3.86 mg), catechol (9.50 mg) and L-Dopa (7.53 mg) [17]. Acetone extract of acacia species effectively reduced oxidative stress induced by H_2O_2 and can be useful as a therapeutic agent to prevent oxidative stress-mediated diseases [4]. The methanol extract of aerial parts of *A. ferruginea* exerts protective effect against ulcerative colitis via antioxidant balance. The study concluded that this may be attributed to the presence of catechins and coumarin derivatives present in the extract [20,21].

Anti-bacterial and anti-fungal activity

Since, antimicrobial efficacy of plant extracts and phytochemicals with susceptible and resistant antibiotics was assessed, the plant-derived antibiotics addressed a new chapter in the field of pharmacology [22,23]. Using different modes of actions phytochemicals showed effective antibacterial actions against susceptible and aggressive pathogens [24]. Significant antibacterial activity was shown by aqueous and methanol extracts of *A. ferruginea*, leaves against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, Salmonella typhi, Staphylococcus aureus and *Streptococcus faecalis* [25]. Moderate activity was observed in *Bacillus subtilis*, *Staphylococcus aureus*, *E. coli*, *Aspergillus niger*, *Aspergillus flavus*, Rhizopus nigricans from leaf hydroalcoholic extract with Zone of Inhibition of 18.0 ± 0.20, 13.0 ± 0.44, 13.0 ± 0.72, 23.0 ± 0.52, 20.0 ± 0.58, 23.5 ± 0.80 [8]. Antifungal activity of aqueous extract of *A. ferruginea* leaves against the fungi *Fusarium verticillioides* at 2 mg/ml showed moderate activity but methanol extract showed good activity with 52.8 ± 0.29% inhibition [25]. Kota et al. reported that the methanolic polyherbal extract containing *A. ferruginea*, showed good anti-bacterial activity against *P. aeruginosa* and *E. coli* with a ZOI of 2.57 ± 0.39, 2.92 ± 0.29 [20].

Anti-cancer activity

Evidence on potent anti-tumour activity of *A. ferruginea* extract in vivo was first reported by Sakthivel et al. [26]. Treatment with methanol extract of aerial parts of *A. ferruginea* significantly reduced the lung collagen hydroxyproline, hexosamine, uronic acid, sialic acid and gamma-glutamyl transpeptidase content and inhibited the iNOS and COX-2 level. *A. ferruginea* suppressed the nuclear factor kappa B (NF-κB) activation and significantly decreased the level of pro-inflammatory cytokines. Reduction in the number of tumours directed capillaries was observed from angiogenesis studies. Sakthivel et al. declared that it could be a promising candidate for the development of metastasis-focused anti-cancer agents that further help to fight melanoma with an effective therapy approach [26]. Sakthivel et al. study revealed that *A. ferruginea* **e**xtract significantly increased the life span, total white blood cell (WBC) count and haemoglobin (Hb) content and decreased the level of Serum Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), gamma glutamyl transferase (γ-GT) and nitric oxide (NO) in DLA bearing cites in tumour models [13]. Strong immunostimulant activity also noted for this extract. The lifetime of mice was enhanced when treated with methotrexate was 79%. The whole study reported that both the extract and standard drug significantly prevented the anemic condition (Hb values of, respectively, 14.6 ± 0.4 and 14.6 ± 0.4% on day 15) which may be due to high content and synergistic activity of specific constituents such as flavonoids, phenolics, steroids, terpenoids, alkaloids, saponins, quinones and tannins present in the leaves.

Anti-diabetic activity

The methanol extract of *Acacia ferruginea* stem bark possess significant antidiabetic activity and justifies the use of the plant for treating diabetes as suggested in folklore remedies. It exhibited reduction in blood glucose concentration in a dose dependent manner compared to the standard drug metformin (250 mg/kg) in normoglycaemic test, oral glucose tolerance test and hyperglycaemic studies. The acute toxicity studies revealed no signs of mortality in animals treated with a single dose of 2000 mg/kg body weight. The study revealed that similar mode of action as alloxan was suggested by relative effect of metformin and it permanently eliminates pancreatic ß-cells and the extract decreases blood sugar levels in alloxanized rats, suggesting extra pancreatic effects of the extract [26].

Analgesic and anti-inflammatory activity

Inflammation is a host's local defense response to cell injury or infection and long-term inflammation may lead to many disorders and pathogenesis. Identifying natural phytoconstituents that can inhibit inflammatory mediators can lead to anti-inflammatory therapies. Hydroalcoholic extract of *A. ferruginea* leaves at a dose of 400 mg/kg had significantly (74.68%) inhibited the inflammation compared to indomethacin (82.8%). Hydroalcoholic extracts of bark and leaves have central analgesic and peripheral analgesic effects, and significantly reduced the paw edema [11]. Sakthivel et al. study revealed that *A. ferruginea* **e**xtract was protective against ulcerative colitis (UC) [27]. Another study in which anti-inflammatory activity pre-treatment with methanol extract of *A. ferruginea* aerial parts (10mg/kg of BW) for 5 consecutive days via intraperitoneal (IP) administration significantly inhibited subsequent

induction of paw edema in both mice models with results comparable to that of indomethacin. *A. ferruginea* extract significantly inhibited Nitric Oxide (NO) synthesis, diminished inflammation and significantly scavenge free radicals generated as in DPPH and NO radical generating assays [5]. Hydroalcoholic extract of the bark of *A. ferruginea* at the dose of 50 mg/kg (6.10 ± 0.30) and leaves at a dose of 100 mg/kg (5.72 ± 0.39) exhibited significant analgesic activity after 45 min. Hydroalcoholic extract of both bark (90%) and leaves (90.91%) showed maximum protection from acetic acid at the dose of 100 mg/kg as compared to standard drug (50.91%) at a dose of 5 mg/kg. The nitrite level was reduced to 29.43 and 28.01 mmol/L (at 75.0 mg/mL) by methanol extract of *A. ferruginea* aerial parts. The IC50 values of acetone extracts of *A. ferruginea* aerial parts was 51.87 mg/mL [18].

Anti- haemorrhoidal activity

Faujdar et al. concluded that the hydroalcoholic extract of bark of *A. ferruginea* significantly reduced the inflammatory cytokines and confirmed as an anti-hemorrhoidal agent by molecular docking and structure-based pharmacophore mapping [28]. This potential activity may be attributed to the presence of potent antioxidants especially flavonoids. It was confirmed by significant reduction in the levels of inflammatory markers like prostaglandins, leukotrienes interleukins.

Other activities

Anti-neoplastic drug Cyclophosphamide (CTX) can cause adverse side effects including immunotoxicity and urotoxicity. *Acacia ferruginea* found to be capable of protecting mice from / mitigating toxicity caused by CTX. Methanol extract of *A. ferruginea* aerial parts (10mg/kg BW, IP daily) reduced CTX (25 mg/kg BW, IP daily)-induced toxicity when administering for 10 consecutive days and the extract also prevented decreases in organ (liver, kidney, spleen, thymus) weight as well as body weight, thereby lessening the potential impact of CTX on the host immune system. The bladder, small intestine morphology and antioxidant (glutathione) levels have been improved in the bladder, indicating a role of the antioxidant in reducing urotoxicity induced by CTX. Moreover, the use of the extract significantly increased total leukocyte counts and bone marrow cellularity/-esterase activity in CTX-treated mice which suggested a protective effect on the hematopoietic system [29]. Vahita et al. reported that *A. ferruginea* extract showed larvicidal efficacy on Culex quinquefaciatus with LC_{50} values as 362.6 ppm [30]. The therapeutic potential and the respective details of *A. ferruginea* are presented in the Figure 1 and Table 1 respectively. Structures of the phytochemicals from *A. ferruginea* are shown in Figure 2.

Figure 1: Therapeutic potential of *Acacia ferruginea.*

Table 1: Review on *Acacia ferruginea.*

S. No	Plant part used	Solvent	Extraction method	Active components	Discussion
	Aerial parts	Methanol	Soxhlation	-	Treatment with AFE significantly decreases the lung collagen, hydroxy proline, hexosamine, uronic acid, sialic acid inhibits i NOS, COX-2 level, decrease the no of p53 and BCl2 positive immunoreactive cells Decreases the level of proinflammatory cytokines and VEGF.
	Aerial parts	Methanol	Soxhlation	-	Showed potent AO& Anti-inflammatory effects Maintains oxidative homeostasis & inhibiting NO synthesis Potential plant-based medication against inflammatory disorders
	Aerial parts	Methanol	Soxhlation	-	Protective action against UC via modulation of oxidation, antioxidant balance, inhibition of inflammatory mediators due to presence of catechins and coumarin derivatives
	Aerial parts	Methanol	Soxhlation	-	Significantly increased total leukocyte counts Protective effect on hematopoietic system, cyclophosphamide (CTX) induced toxicities in mice models
	Aerial parts	Methanol	Soxhlation	Alkaloids, Flavonoids, Saponins, Anthraquinones, Tannins, Glycosides Triterpenoid, Phenolic compounds Derivatives of quinone, Quinoline Imidazole, Pyrolidine, Cyclopentenone	Effective in inhibiting inflammation and tumor progression in vivo. Significant reduction in intracellular GSH levels in DLA cells, 63% increase in life span and prevented anaemic condition
	Bark	Pet ether 70% methanol Distilled water	Soxhlation & Maceration	Alkaloids, Flavonoids Saponins, Tannins, Triterpenoid Phenolic compounds	Hydroalcoholic extract of bark of AF significantly reduces inflammatory cytokines, Anti-hemorrhoidal activity may be attribute to the flavonoids
	Bark	Pet ether Acetone	Soxhlation	-	Significantly upregulated the expression of Antioxidant enzymes in a concentration dependent manner Effectively inhibited H2O2 mediated oxidative stress Useful as a therapeutic agent in preventing oxidative stress mediated diseases
	Bark	Acetone, Hexane, EA, n-butanol	Maceration & Successive partition	-	EA fraction of AF bark possessed higher AO& anti-ulcerogenic activities
	Bark	Pet ether Acetone Methanol	Soxhlation	-	Acetone extracts of AF bark exhibited higher contents of total phenolics, flavonoids
	Bark & leaves	70% methanol	Soxhlation	Alkaloids, Flavonoids, Saponins, Tannins, Triterpenoid, Phenolics	Bark extract revealed central analgesic activity and leaf extract showed peripheral analgesic activity due to more flavonoids and terpenoids. Leaf ext showed good anti-inflammatory activity than the bark. Both exhibited significant analgesic and anti-inflammatory activity
	Bark &fruit	Methanol	Maceration	Alkaloids, Flavonoids, Saponins Tannins, Triterpenoid, Phenolics	Polyherbal extract containing AF got good anti -bacterial activity against gram positive and gram -negative bacteria
	Leaves	Methanol	Soxhlation	-	Larval mortality was observed only after 24hrs of treatment
	Leaves	Ethanol (95%) & distilled water 70:30	Maceration	-	Moderate antibacterial activity against tested bacterial and fungal specimens
	Leaves	Distilled water Pet ether, chloroform Methanol, ethanol	Maceration Soxhlation	-	Methanol and aqueous extracts showed promising anti-bacterial and antioxidant activity

	Leaves	Distilled water Pet ether, toluene, chloroform methanol, ethanol	Maceration Soxhlation	-	Methanol extract of AF inhibits FB1 production Moderate antifungal activity by aqueous extracts of AF
	Leaves Bark Pods	Water 80% methanol 70% acetone 50% DMSO	Boiling -10 min's	-	High extractive values
	Plant material	Methanol	Soxhlation	Polyherbal extract	At lowest conc. only PHE scavenges 50% of radicals compared to standard and PHE has more AO activity compared to standard.
	Seed	50%methanol 70%acetone	Dry heated, pressure cooked Shaken - rotary	-	Dry heated samples of AF seeds showed higher reducing ability and higher hydrogen donating ability than positive standards like ascorbic acid etc. Radical scavenging activity also higher pressure cooking of AF seeds marginally enhanced iron chelating effect than raw samples.
	Stem bark	Pet ether Acetone	Soxhlation	Catechin, Procyanidin B1 Quercetin, 3-O-methyl quercetin, Genistein, Dihydroxy chalcone, Ellagic acid, Ferulolylquinic acid, N-ferulolylglycine, N-ferulolyl glycine isomer, Rosmanol	Decreased LPS induced NO production, expression of inducible NO synthase.AF bark extract revealed the presence of 12 different phenolic compounds
	Stem bark	Pet ether-defatting (40-60) Methanol	Soxhlation	Alkaloids, Flavonoids, Saponins Tannins, Triterpenoid Phenolics, Gums, Mucilages, Carbohydrates	Stem bark possess significant anti-diabetic activity No signs of mortality from acute toxicity studies

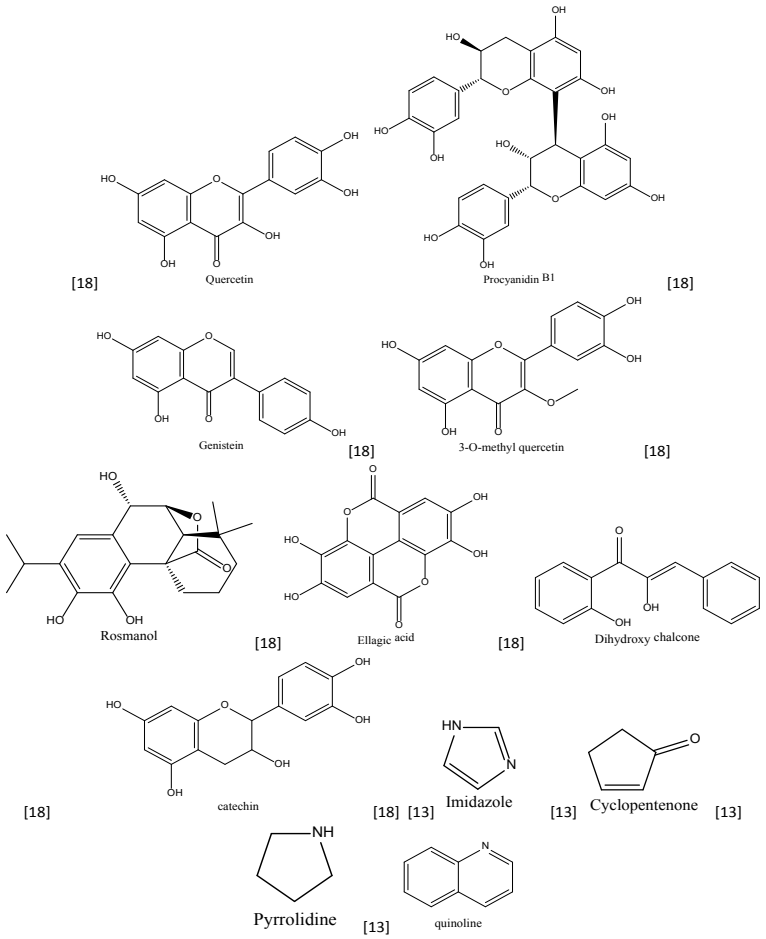

Figure 2: Phytochemicals from *Acacia ferruginea.*

Conclusion

As plants are the ultimate sources of drug development, researchers and pharmaceutical companies can take a lead on *A. ferruginea* since it exhibits anti-cancer, anti-inflammatory, antioxidant, anti-diabetic activity and so on. Focusing on the assessment of bioactive natural products of *A. ferruginea*, and further experiments on suitable models to examine the toxicity and therapeutic uses may contribute to find new drugs.

Declarations

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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