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Review

Bioefficacies of *Cassia fistula:* An Indian labrum

M. Moshahid A. Rizvi*[1,2], Irshad M.[1], Gamal El Hassadi[2] and Salaem Ben Younis[2]

[1]Genome Biology Laboratory, Department of Bioscience, Jamia Millia Islamia, New Dehi-110025. India.
[2]Department of Laboratory Medicine, High Institute of Medical Technology Derna, Libya.

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Cassia fistula **Linn, a semi-wild Indian labrum has been used in the treatment of various diseases in different parts of the world since time immemorial. In Indian literature there has been multiple descriptions regarding its usefulness in the treatment of various diseases. Some authors have reported its antibacterial, antioxidant, hepatoprotective and hypoglycemic potentials. Many other authors have indicated towards the free radical scavenging and antioxidant potential of *C. fistula* both *in vitro* as well as *in vivo*. Despite this valuable available information on this plant there appears a vast virgin area of research on this plant to find out the real natural treasure. The antioxidant and hepatoprotective nature of *Cassia fistula* seems to depend on the total phenolic, proanthocyanidin and flavanoid contents of this labrum. This paper reviews all the experimental studies so far performed on *C. fistula.* This is likely to have important implications on designing any future research on this plant for their potential utility in herbal drug system or in nutritional supplements.**

Key words: *Cassia fistula* Linn, antibacterial, antioxidant, hepatoprotective, hypoglycemic.

INTRODUCTION

Plants are natural reservoir of medicinal agents almost free from the side effects normally caused by synthetic chemicals. A numbers of modern drugs have been isolated from natural sources and many of these isolations were based on the uses of the agents in traditional medicine. One such potential plant is *Cassia fistula* Linn (Hindi-Amaltas, English-Golden shower, Indian labrum), a member of *Fabacea* (alt. leguminasae) family. It is a native of India (Chatterjee and Pakrashi, 1992; Chopra, 1956; Kirtikar and Basu, 1975). It is also grown in Mauritius, South Africa, Mexico, Brazil, China, Nepal, West Indies and East Africa as an ornamental plant due to its beautiful bunches of yellow flowers (Allen and Allen, 1981; Trease and Envas, 1985; 1992; Bahorun et al., 2005). *C. fistula* has been used in the treatment of various ailments in ancient India, dating back to S*ushruta Samhita* and C*haraka Samhita* (Nandkarni, 1954; Kritikar and Basu, 1975). Both the leaves and pods were widely used in traditional medicine as strong purgatives and laxatives (Kirtikar and Basu, 1975; Elujoba et al., 1999) due to presence of sennoside (Van, 1976) and rhein (Index, 1996). In Ayurvedic medicinal system, *C. fistula* was used against various disorders such as haematemesis, pruritus, leucoderma, diabetes and other ailments (Satyavati and Sharma, 1989; Alam et al., 1990; Asolkar et al., 1992). The leaves are known for their laxative, antiperiodic, ulcer healing and anti-rheumatic properties. Leaves were also found effective against cough and ringworm infections (Chopra, 1956; Biswas and Ghose, 1973; Kritikar and Basu, 1975). In Srilanka, *C. fistula* is used in treating bone fracture (Ekanayak, 1980). Pod was reported to have very low level of toxicity (50% lethal dose (LD_{50}) = 6600 mg/kg bw) and no pathological effects

*Corresponding author. E-mail: - rizvi_ma@yahoo.com, irshad_bioscience@yahoo.co.in. Tel :(91) 09911661657/ (218)914556067.

Index: **AAPH**: 2, 2-azo-bis-(2-amidinopropane) didydrochloride, **AE**: Aqueous extract, **AlcE**: Alcoholic extract, **ALP**: Alkaline phosphates, **BHT**: Butylated hydroxytoluene, CE: Chloroform extract, D**CME**: Dichloromethane extract, **DEE**: Diethyl ether extract, **DEN**: Diehylenitrosamine, **DPPH**: 1, 1-diphenyl-2-picrylhydrazyl-2-picrylhydrazyl, **EAE**: Ethyl acetate extract, **EE**: Ethanolic extract, **FRAP**: Ferric reducing antioxidant power, **HE**: Hexane extract, **MDA:** Malondialdehyde, **ME**: Methanolic extract, **PEE**: Petroleum ether extract, **SGOT**: Serum glutamate oxalacetate transaminase, **SGPT**: Serum glutamate pyruvate transaminase, **TEAC**: Trolox equivalent antioxidant capacity

were seen on liver, kidney and rat's testis (Akanmu et al., 2004).

Extensive studies have been carried out during the past few decades on isolation and characterisation of chemical constituents of various parts of *C. fistula.* Lal and Gupta, (1972) isolated rhein, glucose, sucrose and fructose from the fruit pulp and galactomannans from the seeds. Agrawal et al. (1972) isolated fistulic acid from the pods, kaempferol and a leucopelargonidin tetramer having free glycol unit, from the flowers. Kuo et al. (2002) have isolated and identified oxyanthraquinones, chrysophenol and chrysophanein from the seeds. Oxyanthraquinone and dihydroxyanthraquinone from bark (Rani et al., 1998), (-) epiafzelechin, (-) epiafzelechin-3-O-glucoside, (-) epicatechin, procyanidin B_2, biflavanoids, triflavonoids, , rhein glucoside, sennoside A and B, chrysophenol and physcion from leaves (Kashiwada et al., 1996; Kaji et al., 1968; Mahesh et al., 1984), kaempferol, leucopelargonidin tetramer, rhein, fistulin and triterpenes from flower (Narayanan and Seshadri, 1972; Kumar et al., 1966). Fistulic acid, 3-formyl-1-hydroxy-8-methoxy anthraquinone, 3B hydroxy-17-norpimar-8(9)-en-15-one, rhein and sennidine like compound present in pod (Modi et al., 1952; Misra et al., 1996,1997; Kapadia and Khorana, 1966), crysophenol in seeds (Khanna and Chandra, 1996) and Rhamnetin-3-O-gentiobioside in roots (Vaishnav and Gupta, 1996). Pulp has been reported to contain a high concentration of soluble sugar, sucrose, fructose and glucose and rich source of macromineral elements, calcium and potassium (Barthakur et al., 1995).Extensive studies have been carried out on its medicinal values and the synergistic actions. Patel et al. (1965) reported analgesic and antipyretic action. Mazumdar et al. (1998) reported sedative and analgesic action of *C. fistula* seeds. El-Saadany et al. (1991) reported anti-hypercholesterolemic potential of its seeds and very recently, Gupta et al. (2009) have reported hypolipidemic activity of *C. fistula* legume. Methanolic extract of leaves was also found to have a significant anti-cough effect in experimentally induced cough reflex in mice (Bhakta et al., 1998a). Oral administration of ethyl acetate extract of fruits and aqueous extract of seeds reduced uterine implantation and suppressed pregnancy in rats (Bharadwaj and Mathur, 1979; Yadav and Jain, 1999). The fruit of C*. fistula* combination with amoxicillin (Amoxy-cassia) have been reported to have immunomodulatory effect on humoral immune system in BALB/c mice (Ali et al., 2008). It has also been reported for anti-inflammatory (Suwal, 1993), hypoglycemic activity (Alam et al., 1990; Esposito et al., 1991), antiperiodic (Kashiwada et al., 1990), anti-rheumatic (Suwal, 1993), anti-tumor (Bodding, 1983; Gupta et al., 2000), hepatoprotective (Bhakta et al., 1999), antioxidant (Luximon-Ramma et al., 2002; Sidduraju et al., 2002), anti-fungal and anti-bacterial activities (Patel and Patel, 1956; Ramakrishna and Indragupta, 1997; Dhar and Qasba, 1984; Perumal et al., 1998). Beside its pharmacological studies, *C. fistula* seed extract demonstrated ovicidal effect on *Corcyra cephalonica* (rice moth) (Dwivedi and Alka, 2006). The methanol extract of bark reported juvenile hormone-like activity; inhibited metamorphosis of *Disdercus koenigii* Fab at varying degrees and hence made them incapable of reproduction and long life (Jaipal et al., 1983). However, leaf extract significantly reduce the egg laying and fecundity of *Callosobruchus maculates* Fab (Raja et al., 2000) and hence is recommended as a pest control agent. The various medicinal implications have been mainly attributed to the presence of alkaloids, triterpene derivatives, anthraquinone derivatives, polyphenolics, comprising flavanoids, catechines and proanthocyanidins (Agrawal et al., 1972; Morimoto et al., 1988; Kashiwada et al., 1990).

Antimicrobial properties of *C. fistula*

Patel and Patel, (1956) had tested the antibacterial potential of *C. fistula* pulp and seed. The dealcoholized extract of the pulp showed greater effect on gram-positive bacteria than the aqueous extract, while in the case of gram negative bacteria both kind of extract show similar effect. The pattern of effect in the case of dealcoholised seed extract on gram positive and gram negative bacteria was not different. However aqueous extract of seed was only effective against *C. diphtheria* and *S. typhi.* Furthermore, it was observed that the action of dealcoholized extract of pulp was equivalent to about 2.5 units of penicillin sodium in case of *Micrococci*, about 10 units for *B. megatherium* and *C. diphtheria* and about 200 units of dihydrostreptomycine for *S. typhi* and *E. coli*. The action of dealcoholized extract of seeds was equivalent to 0.5 - 1.5 unit of penicillin sodium against all gram positive organisms and 100 unit of dihydrostreptomycine in case of *E. coli* and *S. typhi*. The aqueous extract of pulp showed an activity corresponding to 2.5 unit of penicillin sodium for *M. pyogenes*, 1.5 units for *M. citreus* and *C. diptheriae*, 5 -10 unit for *B. megatherium* and more than 200 units of dihydrostreptomycine sulphate on *E. coli* and *S. typhi*. Aqueous, diethyl ether, ethyl acetate, dichloromethane and methanol extract of leaves are reported to have significant zone of inhibition against *Escherichia Coli, Klebsella aerogenes, Protious vulgaris,* and *Pseudomonas aerogense* bacteria in concentration dependent manner (Perumal et al., 1998). Dichloromethane extract showed maximum zone of inhibition against *E. coli* as well as *P. vulgaris,* while methanolic extract on *P. aerogense*. The aqueous extract of leaves showed an equal effect on tested microorganisms and their anti-bacterial activity increased with increasing extract concentration. Abbas et al. (2004) have reported antibacterial activity of petroleum ether, methanolic and ethyl acetate extract of seeds, stem bark and leaves against *B. subtilis, B. megaterium, S. β- haemolyticus, S. aurus, S. lutea, S. sonnei, E. coli, K. sps, S. shiga, S. boydii, S. flexnerae, S. dysenteriae, S. typhi* and *P. aeruginosa.* The stem bark and

and pod were more active against all tested bacteria. Petroleum ether and ethyl acetate extracts of leaves show activity against all tested bacteria but methanol extract was active only against only *B. megaterium, S. β-haemolyticus, S. typhi* and *P. aeruginosa.* These findings were also supported by Yogesh and Mohan, (2006) and Muthusamy et al. (2006). In another experiment methanolic extract of *C. fistula leaves exhibited more effects on S. paratyphi, B. cereus, B. subtalis, B. megaterium* and *E. coli while P. aeruginosa, K. nemoniae, E. facalis*, *M. luteus, S. aureus, S. epidermidis,* and *S. typhi* were less affected (Yogesh and Mohan, 2006). Hence, alcoholic extract of *C. fistula* leaves show greater zone of inhibition for *S. aureus* and *P. aeruginosa* (Muthusamy et al., 2006). Hexane, chloroform, ethyl acetate, methanol and water extract of flowers demonstrated antibacterial activity against *S. aureus, S. epidermidis, B. subtilis, E. faecalis* and *P. aeruginisa* (Duraipandiyan and Ignacimuthu, 2007).

Ethanolic extract of pod and stem bark of *C. fistula* were found active against *Ranikhet disease virus* (RDV) and *Vaccini virus* (Dhar et al., 1968), Ethanol extract of fruit reported active against Foot and Mouth Disease Virus (FMDV) (Narong et al., 2007). Methanolic extract of leaves inhibit *Venturia inaequalis* in agar nutrient medium but similar effect was not observed by the methanolic extract of pod (Dhar and Qasba, 1984). Aqueous and alcoholic extract of leaves and bark did not show any effect on *Trichophyton metagraphyte* and *Tricophyton simmi* in infected goat and rabbit respectively (Ramakrishna and Indragupta, 1997). Petroleum ether, ethyl acetate and methanolic extract of leaves were active against tested fungi *P. notatum, A. niger, T. viride, A. flavus* and *C. albicans* (Duraipandiyan and Ignacimuthu, 2007). Under the same study, petroleum ether extract of stem bark was also shown to be active against *T. viride, C. albicans, H. californica,* and ethyl acetate extract against *A. niger, T. viride, A. flavus, C. albicans, H. californica* whereas, methanolic extract against *P. notatum, T. viride, A. flavus,* and *H. californica.* The petroleum ether, ethyl acetate and methanolic extract of pod were comparatively more active against *P. notatum, A. flavus* and *C. albicans.* Methanolic extracts from leaves of *C. fistula* was the most potent inhibitor of *P. marneffei.* It was also inhibited *M. gypsums* conidial germination, hyphal growth (Phongpaichit et al., 2004). Over all antifungal activity of *C. fistula is* due to the presence of 4-hdroxy benzoic acid hydrate (Duraipandiyan and Ignacimuthu, 2007).

Methanolic extract of fruit showed anti-leishmanial activity against the promastigote form of *Leishmania chagasi,* presented 50% inhibitory concentration (IC_{50} = 10.03 µg/ml), and intracellular amastigotes demonstrated IC_{50} value of 18.10 µg/ml (Patricia et al., 2007). In same experiment, clerosterol compound isolated from fruit, which infer IC_{50} of 10.03 µg/ml against *L. chagasi* promastigot, 18.10 µg/ml for intracellular amastigotes and recommended as antileishmanial compound. Ali et al. (2007) formulated a noble combination of aqueous fruit extract (3% w/v) and amoxicillin (0.3% w/v), named as Amoxy-Cassia, which was found active against multi-drug resistant *Salmonella enterica, serover Typhi*. The Amoxycassia was found non toxic at 1 gm/body weight in mice (Ali et al., 2007).

Antioxidant, hepatoprotective and anti-inflammatory properties of *C. fistula*

Natural antioxidants play a key role in health maintenance and prevention of the chronic and degenerative diseases, such as atherosclerosis (Parthasarathy et al., 1998), cardiac and cerebral ischema (Keller et al., 1998), carcinogenesis (Kamat et al., 2000), neurodegenerative disorders (Perry et al., 2000), diabetic pregnancy (Viana et al., 2000), rheumatic disorder (Hanninen et al., 2000), DNA damage and ageing (Hu et al., 2000). The antioxidant properties of different extracts of *C. fistula* have been reported, both *in vitro* and *in vivo*. The *in vitro* 1, 1-diphenyl-2-picrylhydrazyl-2-picrylhydrazyl (DPPH) radical scavenging and deoxyribose damage protection properties were reported by Chaminda et al. (2001) using aqueous extract of *C. fistula* root. They showed 50% effective concentration (EC_{50}) of 59 ± 2.7 µg/ml and 30% protection against deoxyribose damage at a concentration of 125 µg/ml. Siddhuraju et al. (2002) calculated DPPH radical scavenging activities in order, stem bark (93%), leaves (74.9%), butylated hydroxytoluene (BHT) (37.8%), flowers (33.2%), pulp (15.7%) and noted that it was directly proportional to total phenolic content in its extract. The elevated DPPH radical scavenging ability of the stem bark and leaves extract might be due to the presence of high concentration of tannins, proanthocyanidins (Kashiwada et al., 1990), flavonols and xanthones (Gupta et al., 1990). The DPPH scavenging activities indicated the ability of *C. fistula* extracts to act as radical scavenger and metal quencher thereby, protecting free radical mediated damage.

Trolox equivalent antioxidant capacity (TEAC) and Ferric reducing antioxidant power (FRAP) assays showed that the reproductive organs of *C. fistula* have highest antioxidant properties compare to vegetative part (Luximon-Ramma et al., 2002). The antioxidant activities were found in the following order: pod > flower > stem bark > leaves and it was also directly proportional to the content of total phenols, proanthocyanidins and flavanoids in its extract (Luximon-Ramma et al., 2002). The pod had the highest antioxidant potential with a TEAC value of 992 ± 0.4 and a FRAP value of 811 ± 23 µmol/g dry weight and correlation coefficient between total phenols and antioxidant capacity was r = 0.989 for TEAC and 0.951 for FRAP (Luximon-Ramma et al., 2002). Sidduraju et al. (2002) recorded antioxidant activity of methanolic and ethanolic extract of different parts of the plant in order of stem bark > leaves > flower > pulp since they

yielded highest concentration of total phenolics (69.4%) in stem bark and lowest in pulp (2.12%). The stem bark extract also exhibited greater peroxidation inhibiting activity on linoleic peroxidation system and liposome peroxidation system followed by leaves. Compared to standard (BHA 87%) 0.2 mg/ml of all plant extracts inhibitted peroxidation activity between 37 and 62%, with significant activity of stem bark $p < 0.05$ (Sidduraju et al., 2002). Very recently, Suresh et al. (2008) also reported lipid peroxidation inhibition of leaves extract. Bark extract found to have radical scavenging capacity also by inhibiting lipid peroxidation in CCl_4 and $FeSO_4$ induced rat liver homogenate (Raju et al., 2005). They further inferred antioxidant activity in DPPH, nitric oxide and hydroxyl induced assay. The results indicate that some of the bioactive compounds, such as xanthones, flavonols and proanthocyanidins present in the stem bark and leaf extracts, should perform as good singlet oxygen quenchers (Gupta et al., 1990; Kashiwada et al., 1990). The stem bark and leaf extracts exhibited highest superoxide radical scavenging and reducing power than other parts in a dose-dependent manner. This may be due to presence of fistucacidin (flavan 3, 4-diol), the main compound in present in stem bark of *C. fistula* (Jawahar and Gupta, 1972). It contains a 4' ortho-position hydroxyl which provides active hydrogen to take part in reaction to scavenge O_2^-.

The methanolic extract of fruit also has been reported to inhibit 2, 2-azo-bis-(2-amidinopropane) dihydrochloride (AAPH) induced lipid peroxidation in bovine brain phospholipids in a concentration dependent manner with an IC_{50} at 40 µg/ml (Sunil and Muller, 1998). It also inhibited the 5-lipoxygenase mediated peroxidation of arachidonic acid; free-radical induced lipid peroxidation and hence inhibited leukotrienes biosynthesis (Sunil and Muller, 1998). This lends support to the traditional use of this plant for the treatment of rheumatic and inflammatory disease (Ford-Hutchinson, 1989).

Herbal remedies are widely gaining acceptance for the treatment and prevention of various diseases as they often contain highly active repertoire of chemical compounds. Hepatoprotective role is one such area where efficacy of C*. fistula* also has been studied extensively in diehylenitrosamine (DEN) and $ClCl_4$ induced hepatic damages like hapetocellular necrosis, carcinogenesis, neoplastic changes and tumor formation in the liver (Aruoma et al., 1994; Nakae et al., 1997). Oral administrations of ethyl extract of leaves restored three fold elevated malondialdehyde (MDA) (end product of peroxidation of lipid) level, superoxide dismutase and catalase activity in 30 days (Kannampalli et al., 2005). The levels of superoxide dismutase and catalase, which are mutually supportive antioxidant enzymes and provide protection against reactive oxygen species, were found to be maintained by phytochemicals of *C. fistula.* Similarly, oral administration of the ethyl extract of leaves restored the normal values of aspatate, alanine tranaminase, alkaline phosphatase, γ-glutamyl tranferase, lactate dehydrogenase and serum billirubine of serum in diehylenitrosamine (DEN) induced hepatic damage (Kannampalli et al., 2007). Moreover, Serum glutamate oxaloacetate transaminase (SGOT), Serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), and serum billurubin level restored normalcy in CCl_4 induced hepatic damage (Bhakta et al., 1999). Likewise, n-heptane leaves extract significantly decreased the level of SGOT, SGPT, bilirubin and alkaline phosphatase in paracetamol induced hapatotoxicity (Bhakta et al., 2001). Aqueous extract of fruit pulp reported significant (< 0.01) decrease in serum hepatic enzymes and total bilirubin and an increase in total protein. The histological structure of liver further retains to near normal through congestion and regeneration of liver tissue (Das et al., 2008). There was also reduction in thio-barbituric acid reactive substances (Chaminda et al., 2001; Kannampalli et al., 2007).

The increased levels of SGOT, SGPT, ALP, and serum billurubin in serum are indicative of cellular leakage and loss of functional integrity of liver cell membrane (Drotman and Lowhorn, 1978). The recovery of normalcy level of the elevated hapato-specific enzyme confirmed the preventive role of the extraction on liver damage and liver disease.

The anti-inflammatory activities of aqueous and alcoholic extracts of C. fistula bark were studied in sub acute models of inflammation in male albino rats. The extracts were found to possess anti-inflammatory effect in both air pouch granuloma and cotton pellet granuloma models. They also found that both the extracts reduce biomarker enzymes, acid phosphatase, cathepsin-D and alkaline phosphatase in serum (Rajeswari et al., 2006). Oral administration of aqueous and methanol extract of stem bark reduced the weight of cotton pellet granuloma and paw oedema in rats at a significant ($p < 0.001$) level (Raju et al., 2005).

The ethanolic extracts of leaves have also been found to have wound healing activity by tissue rege-neration at the site of wound (Muthusamy et al., 2006; Bhakta et al., 1998b).

Hypoglycemic activities of *C. fistula*

Singh and Bharadwaj, (1975) preliminarily investigated hypoglycaemic effect of seeds in normal rat. The aqueous extract of leaves significantly decreased glycemia ($p < 0.001$) (Esposito et al., 1991). The oral administration of methanol extract of leaves also significantly reduced blood glucose level up to 25.2% ($p < 0.001$) and 45.7% ($p < 0.001$) at the dose of 400 mg/kg and 600 mg/kg respectively at the end of 10 h in alloxan diabetic rats (Bhakta et al., 1997). The, LD_{50} of the extract was found to be 3.5 g/Kg. It reduced blood glucose concentration within two hours and effect was maintained up to ten hours. The result was also supported by Alam et al. (1990).

Conclusion

C. fistula is an important and potential medicinal plant. The available literature has given the substantial evidences on the anti-bacterial activities of its pod and seed extracts. The *in vivo* and *in vitro* studies also point towards good anti-oxidant and hepato-protective potentials of *C. fistula*. The antioxidant properties of different parts depend on total phenolic component present in these extract, hence the plant seems to have a lot of potential to be exploited as possible therapeutic agent in various ailments.

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