Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 3| Issue 3 |JUL-SEP|2013|228-233

Review Article
Biological Sciences

RHUBARB: THE WONDROUS DRUG. A REVIEW

S.Bilal[a*], M.R.Mir[a], J.D.Parrah[b], Brahm.K.Tiwari[c], Vijaya Tripathi[c], Priya Singh[c], Mehjabeen[c], A.B.Abidi[c]

[a]*Vety. Biochemistry, faculty of Vety. Sciences & Animal Husbandry, Sheri Kashmir University of Agricultural Sciences and Technology, Kashmir.190006.India*

[b]*Vety. Surgery & Radiology, faculty of Vety. Sciences & Animal Husbandry, Sheri Kashmir University of Agricultural Sciences and Technology, Kashmir.190006.India*

[c]*Department of Biochemistry & Biochemical Engineering, Sam Higginbottom Institute of Agriculture, Technology & Sciences, Allahabad. U.P.211007. India*

***Corresponding Author Email:** sbilal07@gmail.com, sheikhbilal387@yahoo.co.in

ABSTRACT

Rhubarb (Rheum emodi) is an important medicinal plant, which finds an extensive use in Ayurveda and Unani system of medicine. Rhubarb (Rheum emodi, family Polygonaceae) has been traditionally used as diuretic, liver stimulant, purgative/cathartic, stomachic, Antitumour, anticholesterolaemic, antiseptic, wound healer, antidiabetic and tonic. The most important constituents from rhubarb are the flavonoids, saponins, anthraquinone derivatives such as Chrysophanol, Aloe-emodin, Emodin, Physcion, Rhein and its glycoside, Glucorhein etc. Tannins are also present in rhubarb which includes hydrolysable tannins, containing ester or glycosidic bonds composed of gallic acid, glucose and other monosaccharide's and condensed tannins, derived primarily from the flavone derivatives catechin and leucocyanidin. In the past few years, new components such as sulfemodin8-O-b-D-glucoside, revandchinone-1, revandchinone-2, revandchinone-3, revandchinone-4, 6-methyl-rhein and 6-methyl aloe-emodin have been reported from the same species. It also contains macro and micro mineral elements in the order of K>Ca>Fe>Mn>Na>Zn>Co>Li>Cu. Anthraquinone derivatives show evidence of antifungal, anti-microbial, anti-Parkinson's, anti-proliferative, antiviral, anticancer, immune enhancing, antiulcer and antioxidant activities. This review covers published work on therapeutic uses of different components from rhubarb.

KEY WORDS

Rhubarb, therapeutic uses, anthraquinone, tannins, Minerals, antimicrobial, antioxidant, anticancer

INTRODUCTION

Rhubarb (Polygonaceae) is a perennial stout herb; belongs to a large genus '*Rheum'*. The species is found in the temperate Himalayas, from Kashmir to Sikkim, at an elevation of 2000–3800 m. It is found in the alpine zone on rocky soil, moraines and crevices, between boulder sand near streams in specific pockets. R. emodi is restricted to the temperate, sub-alpine, and alpine zones of the Himalayas. Well drained, porous, humus-rich soil is suitable for its cultivation. It prefers exposed or partially shaded habitat and can be cultivated at an altitudes above 1800 m.The height of herb is about 1.5-3.0 meter and has woody large roots; large leaves & branched leafy stem [1,2].The main parts used as drug are roots and rhizomes. Rhubarb has been cultivated for over 5000 years for its medicinal purposes, originating in the mountains of the North-western provinces of China and Tibet. It is first mentioned in the Chinese herbal Pen-King, which listed it as a purgative and stomachic [3].It reached to the West via Turkey and Russia, and was first planted in England by an apothecary named Hayward in 1777. It soon found its way into the kitchen, where its tart flavour became popular in desserts such as rhubarb crumble, as well as in jams, jellies and sauces. Rhubarb is basically a vegetable but is often thought to be a fruit [4, 5]. Rhubarb stalk can be cooked or eaten raw with some people dipping

raw stalks in sugar in order to remove some of the tartness. It should be noted that generally only the stalk of the plant is edible, as its leaves contain considerable amounts of potassium oxalate that can be sometimes fatal, especially in people with susceptibility to oxalic acids.

Bioactivity

Compounds isolated and estimated in Rhubarb are reported to possess antioxidant, antiulcer antidiabetic, and antimicrobial, antifungal, wound healing, anticancer, hepatoprotective and nephroprotective activities. The reports on pharmacological properties of different constituents from *Rheum emodi* are collected from a large number of published reports.

Antioxidant and anticancer activity

Oxidative stress being one of the primary factors for the development and progression of many life-threatening diseases and disorders like cancer, atherosclerosis, diabetes, hyperlipidaemia, neural degeneration and hepatotoxicity, antioxidants from plant sources may be useful in their prevention and treatment. The commercially available and commonly used antioxidants are usually over shadowed because of their unwanted side effects, toxicity and DNA damage. At present, approximately 25% of drugs in modern pharmacopoeia are derived from plants (phytomedicines) and many others are synthetic analogues built on the prototype compounds isolated from plants. Methanolic and aqueous extracts of the roots of *R. emodi* have been shown to possess antioxidant and anticancer potential [6]. In Chinese folk medicine, *R. emodi* is used in the treatment of cancer, ulcer and liver ailments. The anthraquinone derivatives obtained from the rhizome/root extracts of *R. emodi* are found to possess antioxidant and anticancer activity [7]. The anthraquinone derivatives such as emodin, aloe-emodin and chrysophenol have been shown to act as anti-angiogenic by preventing the formation of blood vessel in zebra-fish embryos [8]. The anticancer effect of rhubarb is attributed to the aloe-emodin which not only inhibited the proliferation but also induced apoptosis of two human cancer cell lines Hep G2 and Hep 3B [9].

Wound healing action

The wound healing potential of rhubarb is attributed to the number of components; emodin, flavonoids, tannins, triterpinoids isolated and identified from the herb. In a rabbit wound model emodin isolated from rhubarb have been reported to up regulate the TGF-β1 mRNA and Smad 2 and 3 protein expression in a concentration dependant manner resulting in early wound healing [10]. Wound healing potential of rhubarb is also attributed to flavonoids as it is known to reduce lipid peroxidation not only by preventing or slowing the onset of cell necrosis but also by improving vascularity. Hence, any drug that inhibits lipid peroxidation is believed to increase the viability of the collagen fibrils by increasing the strength of collagen fibres, increasing circulation, preventing cell damage and promoting DNA synthesis [11]. Flavonoids also act as antioxidant thereby scavenge free radicals and help in the accelerated wound healing by early induction of TNF-α [12,13]. Tannins and flavonoids also promote wound healing process due to their astringent and antimicrobial property which seems responsible for wound contraction and increased rate of epithelialization [14, 15].

Antimicrobial action

A number of bacteria and fungi are resistant to antibiotics, large number of medicinal plants and herbs are being examined for their potential as antimicrobial activity. Emodin, aloe-emodin and rhein the major anthraquinone derivatives isolated from rhubarb have been reported to possess significant antimicrobial activity against four strains of methicillin-resistant Staphylococcus aureus. Rhein has also been shown to possess antibacterial activity against Escherichia coli K12 [16]. Rhein, chrysophenol, physcion and aloe-emodin isolated from rhubarb have been reported to possess antifungal against Aspergillus fumigates, Candida albicans and Cryptococcus neofarmans [17]. Revandchinone-4 has been reported to exhibit good antibacterial activity against some strains of gram positive and gram negative bacteria while revandchinone-1and 3 had moderate antibacterial activity. Revandchinone-1, 3 and 4 also exhibited a moderate antifungal activity against Rhizopus oryzae and Aspergillus niger [18]. The ethanolic extract from rhubarb had been reported to possess promising activity against different strains of H. pylori isolated from gastric biopsy specimens of gastric carcinoma in both *in vitro* and *in vivo* studies [19].

Hepatoprotective and Antidiabetic effect

Liver, the largest organ of the body is primarily concerned with the metabolic activity of organisms. It is the central site for the biotransformation of xenobiotics and therefore involved in the detoxifying mechanism of the body. Liver is responsible for detoxifing the chemical substances in the blood and in this process it is exposed to high concentrations of toxicants and toxic metabolites making it susceptible to injury [20]. The liver damage caused by pathogens as well as chemical agents is of similar nature and a proper treatment regime or plan is absent for both. The fact that reliable liver protective drugs are explicitly inadequate in allopathic medicine [21], exhorted the scientists to explore herbal remedies.

Excessive ethanol consumption leads to cellular proliferation, fibrosis, cirrhosis and cancer of the liver [22]. An essential aspect of alcohol-induced liver injury is an impaired vitamin A nutritional status. Studies in human Hep G2 cells have shown that ethanol is cytotoxic to Hep G2 cells, which are transduced to express P-4502E1 (CYP 2E1) and this toxicity results in the death of cells [23], especially in the liver. The hepatic oxidation of ethanol to acetaldehyde mainly involves the enzyme alcohol dehydrogenase [24] which brings the reduction of NAD+ to NADH [25]. The magnitude of severity of liver by disease or hepatotoxins is generally measured by the level of serum enzymes glutamate pyruvate transaminase (SGPT), glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase(ALP), and bilirubin, albumin, and whole liver homogenate. A large number of medicinal plants and herbs play an important role in health care management universally, and lot of attention is paid towards plant and herbal medicines for treatment of various ailments including hepatopathy. India, being rich in the plant and herbal system of medicine, assigns much importance to the pharmacological aspects of many plants and herbs. A large number of phytoconstituents from various plants and herbs are reported to possess liver protecting activity [26]. At the same time, surprisingly, there are limited plant drugs/formulations to treat severe liver diseases. A few excellent reviews have been published on this subject in the recent past [27]. The extract from the rhizomes of rhubarb has shown significant hepato protective activity and restoration of all marker enzymes near control levels against CCl_4 and Alloxan induced liver injury both in vitro and in vivo using 50 mg/kg and 250mg/kg, oral dose [28,29]. In a number of studies it has been shown that *R. emodi* rhizome extract exhibited antidiabetic activity not only by enhancing the peripheral utilisation of glucose, by correcting impaired liver and kidney glycolysis and by limiting its gluconeogenic process, similar to insulin [30], but also restored all marker enzymes to near control levels in Alloxan induced diabetes in albino rats [29].

Nephroprotective effect

The effect of toxic metals on the kidney has been known for many years and is one of the most common kidney problems and occurs when body is exposed to a drug or toxin [31]. A number of therapeutic agents and antibiotics can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome because an increasing number of potent therapeutic drugs like aminoglycoside, sulphonamides, acetaminophen, antibiotics including penicillin's, acyclovir, pentamidine, sulphadiazine, trimethoprin, tetracyclines,NSAID's:Ibuprofen, Indomethacin, Aspirin etc. Chemotherapeutic agents have been added to the therapeutic arsenal in recent years[32]. Aminoglycoside nephrotoxicity is manifested functionally by decreased urine-concentrating capacity,tubular proteinuria, lysosomal enzymuria, mild glucosuria, decreased ammonium excretion and lowering of glomerular filtration rate [33].Exposure to chemical reagents like ethylene glycol, carbon tetrachloride, sodium oxalate and heavy metals such as lead, mercury, cadmium and arsenic also induces nephrotoxicity. Prompt recognition of the disease and cessation of responsible drugs are usually the only necessary therapy [34].

Nephroprotective agents are the substances which possess protective activity against nephrotoxicity. Medicinal plants have curative properties due to the presence of various complex chemical substances. Early literatures have prescribed various herbs for the cure of renal disorders [35]. Renal disorder primarily denotes failure of the excretory function of kidney, leading to retention of nitrogenous waste products of metabolism in the blood [36]. In addition to this,

there is a failure of regulation of fluid and electrolyte balance along with endocrine dysfunction. The renal failure is fundamentally categorized into acute and chronic renal failure [37]. Acute renal failure (ARF) refers to the sudden and usually reversible loss of renal function which develops over a period of days or weeks while chronic renal failure (CRF) is an irreversible deterioration in the renal function which classically develops over a period of years, leading to loss of excretory metabolic and endocrine functions. The nephroprotective activity on all the segments (S1, S2 and S3) of the proximal tubule of kidney against cadmium,mercury and potassium dichromate-induced nephrotoxicity in rats of alcoholic extract of R. emodi has been established. The effect has been proposed because of the tannins present in the fraction. The nephrotoxicity was induced using cadmium chloride, mercuric chloride, potassium dichromate and gentamicin in rats and monitoring the levels of urea, nitrogen and creatinine in serum [38]. In another study nephroprotective activity was assessed in gentamicin,cisplatin and paracetamol induced renal damage in Wistar rats. The protective property of 70% ethanol extract was assessed by measuring the levels of body weight, blood urea, and serum creatinine, tissue glutathione and lipid peroxidation. The effect has been proposed because of the presence of saponins, cardiac glycosides and triterpenoids in the fraction [39].

The rhubarb has also been reported to have beneficial effects on immune system, acute respiratory syndrome and Parkinson's disease. The ethyl acetate extract of rhizome of *R. emodi* has been reported to possess immuno-enhancing activity on cell lines. The effect is dependent on the dose resulting in the increased release of nitric oxide and cytokine TNF-α, IL-12 and a decrease in IL-10 by RAW 264.7 in macrophage cell lines in the presence of extract alone [40,41]. Emodin, one of the main phytoconstituents in rhubarb has been reported to have inhibitory effect on the interaction of SARS-CoV S protein and ACE2. Emodin has been found to block both the binding of SARS-CoV S protein toACE2 and the infectivity of S protein-pseudotyped retrovirus toVero E6 cells. These findings suggested that emodin is a novel anti-SARS-CoV compound and might be considered as a potential lead therapeutic agent in the treatment of severe acute respiratory syndrome (SARS) [42]. Emodin has also been reported to have inhibitory effects on the monoamine oxidase B on rat brain mitochondria thus can have a potent role in the treatment and prevention of Parkinson's disease [43].

CONCLUSION

Rheum emodi is a medicinal plant of immense importance with large pharmacological applications. Besides having the above mentioned pharmacological properties, it has been used as an ingredient of many herbal formulations, which are used for the cure of various ailments, in particular the regulation of blood pressure, fat, hepatitis, fever and cancer. The plant could be further exploited, in order to isolate the various biologically-active constituents responsible for its activity.

REFERENCES

1. Anonymous, *the Wealth of India* Vol-IX. Publication and Information Directorate (CSIR), New Delhi, (1972)
2. Chatterjee, A. and Parkashi, S. C. *The Treatise on Indian Medicinal Plants* Vol. I, PID, New Delhi, (1991)
3. Foust & Clifford, M. Rhubarb: The wondrous drug. Princeton, New Jersey: Princeton University Press. (1992)
4. Lloyd, J.U. Origin and history of all the pharmacopeial vegetable drugs, Chemicals and properties with bibliography. American Drug Manufacturers Association. (2008)
5. Newby, L. J. The Empire and the Khanate. Leiden, The Netherlands: Koninklijke Brill NV. (2005)
6. Rajkumar, V., Guha, G., Kumar, R.A. Antioxidant and anti-cancer potentials of *Rheum emodi* rhizome extracts. Evidence-based Complementary and Alternative Medicine, doi:10.1093 ecam neq048(2010)
7. Krenn, L., Presser, A., Pradhan, R., Bahr, B., Paper, D. H., Mayer, K. K., et al. Sulfemodin 8-O-b-D-glucoside, a new sulfated anthraquinone glycoside, and antioxidant phenolic compounds from *Rheum emodi*. J Nat Prod. s66: 1107–1109.(2003)
8. He, Z. H., He, M. F., Ma, S. C., & But, P. P. H. Anti-angiogenic effects of rhubarb and its anthraquinone derivatives.J Ethnopharmacol. 121: 313–317. (2009)
9. Kuo, P. L., Lin, T. C., & Lin, C. C. The antiproliferative activity of aloe-emodin is through p53-dependent and p21-dependent apoptotic pathway in human hepatoma cell lines. Life Sciences, 71, 1879–1892. (2002)

10. Tang Tin and Yang Jing. Promoting action of emodin on experimental wound healing and its mechanism in rabbits. Chin. J. Pharmacol Toxicol.20 (2): 112-119. (2006).
11. Getie, M.,Gebre Mariam, T.,Reitz, R. and Neubert, R.H. Evaluation of the release profiles of flavonoids from topical formulations of the crude extract of the leaves of *Dodonea viscoa* (Sapindaceae). Pharmazie.57:320-322. (2002).
12. Uma devi, P. Radioprotective, anticarcinogenic and antioxidant properties of the Indian holy basil. *Ocimum sanctum* (Tulsi). Indian J Expt Biol.39:185. (2001)
13. Goel, A.,Kumar, S.,Singh, D.K. and Bhatia, A.K. Wound healing potential of *Ocimum sanctum* Linn. With induction of tumor necrosis factor-α. Indian J Expt Biol.48:402-406. (2010)
14. Tsuchiya, H.,Sato, M.,Miyazaki, T.,Fujiwara, S.,Tanigaki, S. and Ohyama, M. Comparative study on the antibacterial activity of phytochemical flavonones against methicillin-resistant Staphylococcus aureus. J Ethanopharmacol. 50:27-34. (1996)
15. Scortichini, M. and Pia Rossi, M. Preliminary *in vitro* evaluation of the antimicrobial activity of terpenes and terpenoids towards *Erwinia amylovora* (Burrill). J Appl Bacteriol. 71:109-12. (1991)
16. Hatano, T., Uebayashi, H., Ito, H., Shiota, S., Tsuchiya, T., & Yoshida, T. Phenolic constituents of cassia seeds and antibacterial effect of some Naphthalenes and Anthraquinones on methicillin-resistant Staphylococcus aureus. Chemical and Pharmaceutical Bulletin, 47(8): 1121–1127. (1999).
17. Agarwal, S. K., Singh, S. S., Verma, S., & Kumar, S. Antifungal activity of anthraquinone derivatives from *Rheum emodi*. J Ethnopharmacol. 72: 43–46. (2000).
18. Babu, K. S., Srinivas, P. V., Praveen, B., Kishore, K. H., Murthy, U. S., & Rao, J. M. Antimicrobial constituents from the rhizomes of *Rheum emodi*. Phytochemistry. 62: 203–207. (2003)
19. Ibrahim, M., Khaja, M. N., Aara, A., Khan, A. A., Habeeb, M. A., Devi, Y. P., et al. Antimicrobial activity of *Sapindus mukorossi* and *Rheum emodi* extracts: *In vitro* and *In vivo* studies. World J Gastroent. 12: 7136–7142. (2006)
20. Glaister, J.R.: Principles of toxicological pathology. Taylor and Francis, London,UK. pp. 81-94 (1986).
21. Neha, T. and U.M. Rawal: Hepatoprotective and toxicological evaluation of Andrographis paniculata on severe liver damage. Indian J. Pharmacol. 32: 288-293 (2000).
22. Wang, X. D. Chronic alcohol intake interferes with retinoid metabolism and signaling. Nutrition Reviews. 57: 51–59. (1999).
23. Wu, D., & Cederbaum, A. I. Ethanol-induced apoptosis to stable HepG2 celllines expressing human cytochrome P-4502E1. Alcoholism: Clin and Exp Res.23: 67–76. (1999)
24. Svensson, S., Some, M., Lundsjo, A., Helander, A., Cronholm, T., & Hoog, J. O. Activities of human alcohol dehydrogenases in the metabolic pathways of ethanol and serotonin. Eur J Biochem. 262: 324–329. (1999)
25. Lieber, C. S. Role of oxidative stress and antioxidant therapy in alcoholic and non-alcoholic liver diseases. Adv in Pharmacol. 38: 601–628. (1997)
26. Doreswamy, R., & Sharma, D. Plant drugs for liver disorders management. Ind Drugs. 32: 139–144. (1995)
27. Evans, D. A., Subramoniam, A., Rajashekaran, S., & Pushpangadan, P. Effect of *Tricopuss eylanicus* Gaertn, leaf extract on the energy metabolism in mice during exercise and rest. Ind J Pharm. 34: 32–37. (2002).
28. Ibrahim, M., Khaja, M. N., Aara, A., Khan, A. A., Habeeb, M. A., Devi, Y. P., *et al.* Hepatoprotective activity of *Sapindus mukorossi* and *Rheum emodi* extracts *in vitro* and *in vivo* studies. World J Gastroent.14:2566-71. (2008)
29. Radhika, R.,Ragavan, B.,Sharad Pawar, D. and Sudarsanan, D. Action of Marker enzymes of *Rheum emodi* in Alloxan induced diabetic rats. Asian J. Exp. Biol. Sci. 3 (2):420-423. (2012)
30. Radhika, R., Kumari, D. K., & Sudarsanam, D. Antidiabetic activity of *R. emodi* in Alloxan induced diabetic rats. Inter J Pharma Sci and Res.1:296-300. (2010)
31. Porter, G.A. and Bennett, W.M.Nephrotoxic acute renal failure due to common drugs.American J Physiol. 241(7): F1-F8. (1981).
32. Hoitsma, A.J., Wetzels, J.F and Koene, R.A. Drug induced nephrotoxicity. Aetiology, clinical features and management. Drug Saf. 6 (2):131-147. (1991)
33. Kaloyanides, G. J., & Pastoriza-Munoz, E. Aminoglycoside nephrotoxicity. Kidney International. 18: 571–582. (1980)
34. Paller MS., Drug induced nephropathies. Med Clin North Am.74 (4):909-17. (1990)
35. http://farmacists.blogspot.com
36. Herfindal, Gourley. Text book of therapeutic drug and disease management. 7th Edn. Charcil Livingstone. London. 425-36. (2000)
37. Barry M, Brenner, Floyd C, Rector. The kidney 6th Ed. Vol I, W.B. Saunders Company, Philadelphia. 3-67. (2000).
38. Alam, M. M. A., Javed, K., & Jafri, M. A. Effect of Rheum emodi (Revand Hindi) on renal functions in rats. Journal of Ethnopharmacol. 96: 121–125(2005) .

39. Pramod, Kumar., Devala Rao, G., Lakshmayya. and Ramachandra Setty, S. Nephroprotective and Nitric oxide Scavenging Activity of Tubers of Momordica tuberosa in Rats. Avicenna J Med Biotech. 3(2): 87-93 (2011)
40. Fozia Kounser. And Zargar, M. Afzal. *Rheum emodi* induces Nitric Oxide synthase Activity in murine macrophages. Am J. Biomed Sci. 2 (2):155-163. (2010)
41. Kounsar, F., Rather, M. A., Ganai, B. A., & Zargar, M. A. Immuno- enhancing effects of the herbal extract from himalayan rhubarb *Rheum emodi* wall. ex Meissn. Food Chemistry, 126, 967–971. (2011)
42. Ho, T. Y., Wu, S. L., Chen, J. C., Li, C. C., & Hsiang, C. Y. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Research. 74:92–101. (2007)
43. Kong, L. D., Cheng, C. H. K., & Tan, R. X. Inhibition of MAO A and B by some plant derived alkaloids, phenols and anthraquinones. J Ethnopharmacol.91: 351–355. (2004)

***Corresponding Author:**
S.Bilal
Vety. Biochemistry,
faculty of Vety. Sciences & Animal Husbandry,
Sheri Kashmir University of Agricultural Sciences and Technology, Kashmir.190006.India