International Journal of Research in Medical Sciences
Tewari I et al. Int J Res Med Sci. 2019 Feb;7(2):649-655
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20190375

Review Article

Carcinogenic herbs: a review

Ishan Tewari[1], Prashant Shukla[2]*, Vijay K. Sehgal[1]

[1]Department of Pharmacology, Government Medical College, Patiala, Punjab, India
[2]Drug Safety Physician, Parexel International, Chandigarh, Punjab, India

Received: 09 December 2018
Accepted: 10 January 2019

***Correspondence:**
Dr. Prashant Shukla,
E-mail: dr.prashant.shukla@outlook.com

ABSTRACT

Herbal toxicity is a field that has rapidly grown over the last few years along with increased use of herbal products worldwide. People prefer using herbal medicines rather than allopathic because herbals are considered safe. Use of herbal medicines from ancient times does not ensure their complete safety. With the growing awareness regarding pharmacovigilance worldwide, there has been an increase in the number of reported adverse events occurring with the use of herbal products. The objective of the study is to aware the researchers about most commonly used Indian medicinal herbs inducing carcinogenicity like *Aloe vera*, *Ginkgo biloba*, Kava kava, etc.

Keywords: *Aloe vera*, Carcinogenicity, *Ginkgo biloba*, herbals, Kava kava

INTRODUCTION

Herbal preparations are widely used worldwide for various disease conditions and as food supplements. The herbals are considered as safe as they are used from ancient times. Up to 80% population of developing countries rely on traditional medicines for their primary health care.[1] However, long term use of herbals does not indicate that the herbal preparations are completely safe. There are various cases where herbals have shown toxic effects. In China, there were 9854 known reported cases of adverse drug reactions in the year 2002 due to the use of herbal medications.[1] Cardiotoxicity, hepatotoxicity, nephrotoxicity, etc have been reported by the use of herbal preparations.[2]

In this review article we will discuss the commonly used herbal medications which are carcinogenic. Carcinogenicity is associated with the use of various widely used herbs like *Aloe vera*, *Ginkgo biloba*, Kava kava, Goldenseal, Aristolochia species which are discussed in this review.

REVIEW OF LITERATURE

The databases of PubMed, SCOPUS and Medline were searched using the terms "Aloe vera", "Gingko biloba", "Kava kava", "Goldenseal", "Aristolochia", "Betel quid", "Dong quai", "Comfrey", "*Rubia tinctorum" and "Carcinogenic*" combined with the Boolean operator "AND". The search was repeated using similar terms like herbal drugs, carcinogen and tumorogenic and the results combined. The duplication of articles from the returned reference lists was identified and removed. The final list was consolidated into one list from the three databases.

The abstracts from the final list were downloaded and analyzed if the abstract contained data relating to the carcinogenic potential of the selected herbal drugs. These articles were then downloaded in full and analyzed. In addition, all the selected articles had to be written in English language and accessible either through open access.

DISCUSSION

This review provides insights regarding the carcinogenic potential of some of the most common herbal drugs "Aloe vera, Gingko biloba, Kava kava, Goldenseal, Aristolochia, Betel quid, Dong quai, Comfrey and *Rubia tinctorum* in various cultures and regions across the globe. Various supporting studies have been discussed to reach an unbiased conclusion regarding these drugs. These drugs have been discussed in an orderly fashion below:

Aloe vera

Aloe vera is a perennial, succulent, pea- green colour plant which mainly in the dry regions of Africa, Asia, Europe and America. Its botanical name is *Aloe barbadensis* miller and belongs to Asphodelaceae (Liliaceae) family. Another well-known species of Aloe vera is of *Aloe arborescens* by Miller.[3,4] Aloe vera is known to possess healing properties, anti-inflammatory action, laxative effects, antiviral, antitumor activity, moisturizing effect, anti-ageing effect and antiseptic effect.[3] Various studies have suggested that Aloe vera is associated with carcinogenic properties. Boudreau et al, reported carcinogenicity of extract of *Aloe barbadenis* Miller (Aloe vera) in F344/N rats and B6C3F1 mice. A 13-week exposure of leaf extract of Aloe vera produced goblet cell hyperplasia of the large intestine in both species. Studies of 2-year exposure of Aloe vera on both species revealed the formation of neoplasms and non-neoplastic lesions which were restricted to the large intestine. There was a prevalence of mucosa hyperplasia of the large intestine in F344/N rats, whereas in B6C3F1 mice goblet cell hyperplasia of the large intestine was reported. [4] Yokohira et al. reported equivocal colonic carcinogenicity of *Aloe arborescens* Miller in Wistar Hannover rat in a 2-year study. Histopathological examination of rats revealed ileocecal lymph nodes swelling. There was a noteworthy rise in incidences of the thickening of the epithelium of the colon. Chronic nephropathy in kidneys, more prominent in the case of female groups was observed. Yellow-brown pigmentation in renal tubules was also observed. Non-neoplastic or pre-neoplastic lesions were also seen in the heart, lymph nodes, thymus, parathyroid, nasal cavity, lung/bronchial, salivary gland, stomach, duodenum, urinary bladder, epididymis, ovary, vagina, musculature, skin/subcutis, Zymbal's gland, Harderian gland, and brain but at a lower frequency.[5] Hence, the causal association of Aloe vera with colon and other organs cancer cannot be ruled out, although more studies on humans are required for any final conclusion. However, herbs like Aloe vera should be used carefully.

Ginkgo biloba

Ginkgo biloba is a living fossil which belongs to family Ginkgoaceae.[6,7] It is a widely used herb to treat pulmonary disorders (like asthma, cough, and enuresis), alcohol abuse, and bladder inflammation, treat heart and lung dysfunctions and skin infections.[8] The extracts of Ginkgo biloba contain some hazardous constituents like ginkgolic acids. A study conducted by Hecker H et al confirmed that ginkgolic acids reduce the cell viability as tested against the cell culture of a renal tubular epithelial cell line (derived from a rhesus monkey) and immortalized human keratinocyte cell line.[9] A 3-months study on F344/N rats revealed hepatocyte hypertrophy and thyroid gland follicular cell hypertrophy due to the treatment with *Ginkgo biloba* extract. In the exposure of *Ginkgo biloba* for 3-months on B6C3F1/N mice reported the prevalence of increased hepatocytic hypertrophy along with focal hepatocytic necrosis. In another 2-year study, *Ginkgo biloba* extract exposure studies revealed a raise in levels of thyroid stimulating hormone in rats. Hepatocellular adenoma was also found in *Ginkgo biloba* extract treated rats. Non neoplastic lesions were found along with hepatocyte hypertrophy and bile duct hyperplasia in all dosed groups of males and females, focal fatty change in all dosed groups of females, cystic degeneration, oval cell hyperplasia and necrosis in males. There was a small raise in follicular cell adenoma of the thyroid gland was also found in male and female rats. A noteworthy raise in the prevalence of transitional epithelium and respiratory epithelium hyperplasia was also observed in both male and female dosed groups. Raised goblet cell hyperplasia in the respiratory epithelium and inflammation were noticed. Incidences of mononuclear cell leukemia were also found to be greater than vehicle groups. 2-year exposure of *Ginkgo biloba* extract on mice also demonstrated many toxic effects. There was an increase in the occurrence of hepatocellular adenoma in female groups whereas hepatocellular carcinoma and hepatoblastoma were found in both dosed groups of males and females. Also, in both male and female groups, hepatocellular adenoma or carcinoma (combined), hepatocellular carcinoma or hepatoblastoma (combined), and hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) were observed. Non-neoplastic liver lesions were found to be increased which included hypertrophy along with erythrophagocytosis in dosed groups of males and females, hematopoietic cell proliferation, inflammation, and necrosis in male groups, and cytoplasmic vacuolization, eosinophilic focus, and mixed cell focus in all dosed groups of females. Raised events of inflammation, epithelium hyperplasia, and epithelium hyperkeratosis along with epithelium ulcer in forestomach were also reported. Pigmentation and hyaline droplets were found in the olfactory epithelium.[10]

Rider et al, evaluated the carcinogenic potential of Ginkgo biloba extract B6C3F1/N mice and F344/N rats and concluded liver, thyroid, and nose as targets of Ginkgo biloba extract. Ginkgo biloba extract induced liver tumors in male and female mice and thyroid gland follicular cell tumors in male and female rats. Hepatocyte hypertrophy and enlargement were observed during 3-month studies in rats. Raised incidences of thyroid gland

follicular cell hypertrophy were also observed. The 3-Month exposure studies in mice revealed raised incidences non-neoplastic nasal lesions in male and female mice. Histopathological examination revealed the lesions in the nose of male and female mice had hyaline droplet in the respiratory and olfactory epithelium. In addition this, there was hyaline droplet atrophy and pigmentation in the olfactory epithelium. Hepatocellular adenomas, liver lesions, hepatocyte hypertrophy and bile duct oval cell hyperplasia, necrosis, and cystic degeneration were noted in 2-year exposure study on rats. Also, there was a formation of thyroid follicular cell adenomas and non-encapsulated masses due to the proliferation of follicular cells within the thyroid gland. In the nose, multiple non neoplastic lesions were found. Hyperplasia in transitional and respiratory epithelium, atrophy and metaplasia in the olfactory epithelium, atrophy of nerves in the olfactory epithelium, pigmentation of the olfactory epithelium, chronic active inflammation, and hyperplasia of goblet cells in the respiratory epithelium were noticed to increase in a dose-dependent manner. In a 2-year study in mice, hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma of the liver were observed. A dose dependent increase in non-neoplastic lesions including hepatocyte hypertrophy, erythrophagocytosis, hematopoietic cell proliferation (increased in males, decreased in females), inflammation (males only), cytoplasmic vacuolization (females only), and necrosis was noticed. Raised incidences of hyaline droplet accumulation and olfactory epithelium pigmentation were also found.[11] These studies provide substantial evidence on how *Ginkgo biloba* can produce cancerous lesions but reports of any such events are required in human subjects also for conclusive validation.

Kava kava

Kava kava, a perennial plant, native to the South Pacific and its non-alcoholic extracts are used to treat anxiety, stress, muscular spasms, pain, and menstrual disorders. Its botanical name is *Piper methysticum.*[12,13] Active compounds present in kava kava are known to reduce motor activity and have analgesic, anticonvulsant, and hypnotic properties.[14] Behl et al, reported carcinogenicity due to exposure of Kava kava F344/N Rats and B6C3F1 mice. In the 2-week study, the liver was observed as a target organ of Kava kava. There was also an increase in the prevalence of minimal hepatocellular hypertrophy. In a 3-months study on rats, increased hepatocellular hypertrophy was observed more in female groups than in male groups whereas centrilobular hypertrophy had increased in both males and females. Microscopy examinations of lesions revealed the presence of enlarged hepatocytes, primarily located in the centrilobular regions, which were characterized by increased hepatocellular size and cytoplasmic eosinophilia and decreased cytoplasmic glycogen content. The 2-year exposure study of Kava kava in rats showed the occurrence of non-neoplastic lesions in the livers. Hepatocellular hypertrophy was also observed, which was characterized by an irregular enhancement in the size of hepatocytes, commonly in a centrilobular distribution. Cystic degeneration, that consisted of multilocular cystic areas were also found which contained finely granular or flocculent eosinophilic material, seemingly resulting from the distension and occasional rupture of adjacent hepatocytes. A rare lesion present in the pancreas was also observed, which accompanied the prevalence of metaplasia of pancreatic acinar cells to a hepatocytic morphology. Several neoplastic lesions noted in the livers of mice in the 2-year study. An increase in hepatocellular adenomas and hepatocellular carcinomas was also observed. Hepatocellular carcinomas had neoplastic hepatocytes that exhibited mild to marked cellular and nuclear pleomorphism and mitoses. Centrilobular hypertrophy was also observed which was portrayed by enlargement of centrilobular hepatocytes with raised amounts of eosinophilic cytoplasm and enlarged nuclei. [15] So from above studies it is clear that Kava kava has the potential to induce liver cancers and may affect pancreas too, so it should be consumed carefully.

Goldenseal

Goldenseal, botanical name (*Hydrastis canadensis* L.), is used as an herbal remedy for digestive disorders, urinary tract infection, and upper respiratory inflammation.[16-18] It also exhibits anti-catarrhal, anti-inflammatory, antidiabetic, antiseptic, astringent, laxative, and muscular stimulant properties.[19] Chen S et al, demonstrated the toxicity of the five goldenseal alkaloid named as berberine, palmatine, hydrastine, hydrastinine, and canadine. Comet assay was performed where all the five constituents were treated with HepG2 to evaluate their DNA damaging potential. Among them, berberine, emerged as most potent DNA damage inducer in human hepatoma HepG2 cells whereas, palmatine is placed next to bererine. DNA damaging potential of commercial goldenseal products was also assessed for the extent to cause DNA damage in HepG2 cells. It was found that goldenseal products persuaded DNA damage in liver cell cultures which can be linked to berberine contained in them. Berberine also led to cell cycle arrest as observed in HepG2 cells. It raised the levels of p-Chk1, p-Chk2, and p21Waf1/Cip1, the protein which when increase promotes cell cycle arrest in G1 phase. Evaluation of the activity of five goldenseal constituents on the Topoisomerase I-mediated DNA relaxation of supercoiled plasmid DNA pBR322 revealed that berberine and palmatine inhibited the DNA relaxation activity of Topoisomerase I in a dose-dependent manner but other three did not. Berberine and palmatine considerably inhibited topoisomerase II activity by decreasing the amount of circular decatenated kDNA and increasing the amount of catenated kDNA, in a dose-dependent manner while canadine showed lesser Topo II inhibition. Evaluation of DNA damaging effect of berberine on lentivirus system was also done by doxycycline (DOX)-induced silencing of topoisomerase I

and II in HepG2 cells. This test revealed that the DNA damaging effect of berberine depends on topoisomerase II but not on topoisomerase I.[19] Dunnick et al, studied the carcinogenesis of goldenseal root powder in F344/N rats and B6C3F1 mice. Minimal to moderate hepatocellular hypertrophy was observed in a 2-week study on rats. Minimal hypertrophy of centrilobular hepatocyte was observed in mice during 2-week study. There was a noteworthy rise in liver weights along with hepatocyte hypertrophy in rats which were exposed for 3-months. Similar changes were observed in the 3-months study on mice. 2-year exposure study of goldenseal on rats revealed the presence of hepatocellular adenoma, hepatocyte hypertrophy and raised eosinophilic focus. Incidences of hepatocellular adenoma and hepatoblastoma were also noticed in mice in 3-month exposure study.[20] Hence, it can be concluded that goldenseal may prove as a contributing factor in cancer if not consumed under medical supervision.

Aristolochia

Aristolochia is a traditionally used medicinal herb which is used as the antibacterial, antiviral, antifungal, and antitumor agent. One of its active constituents, aristolochic acid is known to have antibacterial, antiviral, and antifungal.[21,22] Nortier et al, reported urothelial carcinoma associated with the use of a Chinese herb *Aristolochia fanghi*. 18 cases of urothelial carcinoma were reported in which 17 cases were of carcinoma of the ureter, renal pelvis, or both and 1 was of papillary bladder tumour.[23] Schmeiser et al, evaluated the renal tissues from 5 patients with Chinese herbs nephropathy to investigate the presence of aristolochic acid (AA)-derived DNA adducts using 32P-postlabeling assay method. The test revealed the presence of DNA adducts formed by aristolochic acid in renal tissue of all five patients.[24] Nesslany et al, measured DNA fragments produced due to cleavage of DNA single and double strand using comet assay. Aristolochic acid when treated with nuclei isolated from kidney cells, led to fragmentation of DNA.[25] Aristolochic acid also cleaved DNA breakage in a dose-dependent manner when evaluated in vitro in comet assay using HepG2 cells.[26] Li et al, reported the effect of AAI on DNA damage and cell cycle in porcine proximal tubular epithelial cell lines using comet assay. It was observed that AAI-facilitated cleavage of DNA in a dose-dependent manner before apoptosis and lysis in the treated.[27]

Betel quid

Betel quid chewing is widely practised in Taiwan, India, Papua New Guinea, South Africa, and other Southeast Asian countries.[28] Betel quid mainly contains betel leaf, areca nut and slaked lime.[29] Areca nut powder is used as a traditional medication to eliminate tapeworm and intestinal worms. It is also used in some dentrifices.[30] Kaushal et al, had reported the persistence of breast cancer in individuals who chew betel quid.[31] It is also known to induce carcinomas in the liver. Tsai et al, performed a controlled case study and concluded that betel quid chewing play role in inducing hepatocellular carcinoma.[32] Yen et al, evaluated the dose-response relationships of the risk of oral pre-malignant lesions among men who chew betel quid. An assessment of oral pre-malignancy lesions was conducted for early detection of oral pre-malignancy lesions. Studies conducted on 8360 individuals revealed that 491 individuals suffered from leukoplakia, 124 from erythroleukoplakia, 441 from oral submucous fibrosis, and 104 from had lichen planus or other abnormal lesions.[33] Chiu et al, reported enhancement in oral cancer cell migration due to betel quid extract, by the activation of a muscarinic M4 receptor-mediated signalling cascade involving Src family kinases (SFKs) and extracellular signal-regulated kinase 1/2 (ERK1/2). Muscarinic M4 receptor was found to facilitate BQ-induced oral cancer cell migration and activation of ERK1/2. Treatment of Ca9-22 cells with BQ showed SFKs were found to be acting downstream of muscarinic M4 receptor whereas upstream of ERK1/2 in the BQ-activated signalling pathway. Involvement of Muscarinic M4 receptor in BQ-induced oral cancer cell migration was also evaluated by assessing physical interaction between BQ and M4 receptor using competitive receptor-binding assay.[34] Bhide et al, studied the aqueous extract and polyphenol fraction of betel nut in Swiss and C17 strains of mice for carcinogenicity. These studies revealed that tumours of the gastrointestinal tract were present in 58% and 25% of Swiss and C17 mice respectively who were administered with aqueous extract of betel nut. Polyphenol fractions induced tumours at other sites in 17% of the mice. On the other hand, aqueous betel leaf did not induce tumours in treated mice indicating the absence of any carcinogenic constituent.[35] Areca nut which is incorporated in betel quid is known to possess psychoactive properties.[30] Bhavana et al, performed the carcinogenicity studies of areca nut chewers and revealed that there was a noteworthy rise in incidences of sister chromatid exchanges and chromosome aberrations in peripheral blood lymphocytes and the percentage of micronucleated cells in exfoliated cells of buccal mucosa in areca nut chewers. Genotoxicity was mainly induced in oral epithelium.[36] Exposures of areca nut extract oral cancer cells lead to down-regulation of Ches 1 gene expression, which is known to be reduced in oral cancer tissues. Exposures of arecoline, a major alkaloid of areca nut, on Ches 1 gene lead to its inhibition in a time-dependent and dose-dependent manner.[37] Sundqvi et al, performed acute exposure (3hours) of areca nut aqueous extract on cultured human buccal epithelial cells. Studies revealed the formation of ridges in plasma membrane thus showing the presence of internalization of extract particles. Not only that, but DNA breaks were also found due to extract exposure indicating the inhibition of DNA repaired. Another genotoxic agent carcinogen 3-(4-N-nitrosomethyl-amino) propionaldehyde a salivary areca-nut-specific carcinogen was also found to induce the

formation of DNA protein cross-links and DNA single-strand breaks in normal buccal epithelial cells.[38]

Dong quai

Dong quai, botanical name *Angelica sinensis*, is used to treat dysmenorrhoeal, premenstrual syndrome, and menopausal symptoms. Dong quai contains bergaptan, safrole, and isosafrole, compounds that can be carcinogenic. The carcinogenic potential of dong quai remains unknown because it's unclear whether carcinogenic compounds are present enough amounts to cause cancer. However, it is still advised that the patients at risk for cancer, especially hormone-sensitive cancers (breast, uterine, and ovarian cancer, endometriosis, and uterine fibroids), should not use dong quai.[2] In contrast to the above observation, Tsai et al. reported that dong quai has strong activity against glioblastoma both in vitro as well as in vivo.[39] Lin PC et al, further isolated the key components of dong quai which imparts its anti-cancer activity. The major components were found to be BP and K2. BP possesses pro-apoptotic activity in vitro.[40] In the case of Dong quai, both anti-cancer and cancer activity has been reported yet studies have shown its anti-cancer activity, more controlled studies and ADRs are required for any strong conclusion.

Comfrey

Comfrey *(Symphytum officinale*) is a traditional medicinal plant for the treatment of painful muscle and joint complaints. It is found in Europe, North America and some parts of Asia.[41] Mei et al, evaluated the mutagenicity of comfrey root powder in rat liver as it is the target organ for its carcinogenic activity in liver cII gene of Big Blue rats. Mutations were observed in liver cII gene and it was concluded that pyrrolizidine alkaloids present in comfrey lead to mutations and incidences of tumour in rat liver.[42] A study conducted by Hirono et al revealed that comfrey leaves and roots induced hepatocellular adenomas in inbred ACI rats.[43]

Rubia tinctorum

Madder color is used as a food additive in parts of Japan and Korea. Madder color is obtained from the roots of *Rubia tinctorum*. It is also used to treat kidney and bladder stones. Inoue et al, found that madder color has carcinogenic potential against liver and kidneys as tested in F344 rats. Moreover, they also reported that rubiadin (a metabolite of madder color) causes renal carcinogenesis in rats.[44-46] Westendorf et al, reported the mutagenic potential of lucidin (1,3-dihydroxy-2-hydroxymethyl-9,10-anthraquinone), a natural component of Rubia tinctorum L. in five *Salmonella typhimurium* strains where mutagenicity was enhanced when rat liver S9 mix was added to it. Lucidin also introduced breaks in DNA single-strand and induced cross-links in DNA-protein as evaluated using alkaline elution method.[47] Poginsky et al, evaluated DNA binding potential of alizarin, lucidin, a glycoside mixture containing alizarinprimeveroside and lucidinprimeveroside, and Rubia Teep (a herbal drug made from Rubia tinctorum containing lucidin), first by incubating them primary rat hepatocytes for 24h and then analysing the isolated DNA and second by treating Male Parkes mice with them and testing DNA isolated from liver, kidney, duodenum and colon. On DNA analysis using 32P-postlabelling, it came into light that lucidin, the glycoside mixture and Rubia Teep formed DNA adducts in all the tissues whereas Alizarin did not. So, it can be concluded that lucidin is a main carcinogenic constituent in *Rubia tinctorum*.[48] In addition to this, Blomeke et al reported the genotoxic glycosides from metabolism of two anthraquinone glycosides, alizarinprimeveroside (ALP) and lucidinprimeveroside (LuP) present in present in *Rubia tinctorum* L.[49]

CONCLUSION

Traditional medicines including herbal drugs have always been a source of modern day medicines. These medicines are being used in all the areas of therapeutics including infectious diseases, analgesia, cardiovascular disorders, etc. Although herbal drugs have time tested reputation of safety, the modern day healthcare needs a better safety backup rather than rely on folklores. Various in vitro and preclinical studies have questioned the so-called established and implied safety of these herbal drugs. The attributable adverse reactions range from minor to major disabling conditions. Moreover, the knowledge about various drug-drug interactions is largely limited. In addition to this, we found data of herbal carcinogenicity in animals but were not able to find much data on humans. Like we seen in case of Dong quai and Comfrey, very lesser detailed studies were available. Also, adverse drug reactions occurred in human subjects due to herbs were not available to reach a strong conclusion. Hence, more data based on strict pharmacovigilance of these drugs is warranted before its safety for human use is approved. It is advisable to tread the vast knowledge of traditional medicines with caution so as to strengthen the therapeutic armamentarium without risking human lives based upon blind faith.

Funding: Pharmacovigilance Programme of India (PvPI), Indian Pharmacopoeia Commission, Ghaziabad (U.P.), India
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Tewari I, Shukla P, Sehgal VK. Carcinogenic herbs: a review. Int J Res Med Sci 2019;7:649-55.