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A REVIEW ON CARCINOGENIC POTENTIAL HAZARDS OF HERBAL MEDICATIONS

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ABSTRACT

The herbal medication refers to crude drugs of vegetable origin utilized for the treatment of diseases. Generally, the herbs were selected and utilized by nonprofessionals like old persons of home or local herbal practitioners and rarely by recognized herbal practitioners in India. People are using herbal medications not only to cure day-to-day ailments but also to improve body resistance and to improve fitness. The regular and continuous use of herbal medications may cause specific problems over relatively long periods, as many herbs contain various active principles, which may posses some level of toxicity. Thus, it is very important to recognize the potential hazards of various herbs and their medicative preparations. Many plants such as members of Euphorbiaceae, Boraginaceae, Asteraceae etc., contain biochemicals like phenylpropanoid compounds, various acids, tannins and phorbol esters etc., which are carcinogenic and can promote tumor formation.

INTRODUCTION

During late twentieth century herbal medication has acquired a new specialized importance and definition. As far as definition is concerned the term herbal medications or herbs now refers to crude drugs of vegetable origin, which are utilized primarily by lay persons. In India they are rural people, tribal and poor urban families migrated from remote areas, for treatment of day to day ailments. Some elite classes and urban societies were also using herbs rather herbal preparations but before consuming such preparations, they consult recognized medical practitioners of Ayurvedic, Siddha or Unani system of medicine. In these indigenous systems of medicine the herbs have been used in combination and are being processed in various ways before they come into dosage form, therefore, these herbal preparations are comparatively safe and effective in prescribed dosage and are not coming under crude drugs category.

Problem starts with the selection and use of herbs as medicine by unrecognized and nonprofessionals who employ herbs not only to cure diseases but also to improve body resistance. Mostly these local practitioners use herbs to cure sexual disorders and to increase sexual performance, as these herbs have miraculous therapeutic effects and easy availability. On the advice of such practitioners people continue their consumption over relatively long periods. Such chronic utilization for long periods may cause some specialized problems as every crude herbal drug posses some level of toxicity. Thus, it becomes very important to recognize the potential hazards of various herbal medications before administration especially over long-term use.

A common public misconception is that drugs are safe if they are natural herbs or their products whereas they are likely to be hazardous if they are synthetically produced. The idea that “natural is safe” may account in part for public concern about synthetic pesticide residues in the diet vs. public interest in and consumption of medicinal herbs. Medicinal herbs receive little regulatory scrutiny or limits compared to synthetic chemicals such as pesticide residues in preserved foods and soft drinks or pharmaceuticals, even though every chemical is toxic at some dose.

With the coming up of the chemical revolution several medicinal plants of antiquity, which were once used as the traditional medicine, have found wide acceptance and a place of pride in the modern system of medicine. The chemical examination of such herbs revealed that they posses chemical compounds of great biological activity but only a few studies were conducted to interpret long term use of such wonderful herbs and their effect on human body. Carcinogens and cancer promoting substances are of concern to many individuals as about three to seven percent of world population of adults is suffering from cancer or is at a high risk. Many chemical compounds now reported as carcinogens or cancer-promoting chemicals in plants belong to pyrrolizidine alkaloids (Huxtable 1995), phenylpropanoid compounds, aristolochic acid and tannins groups. In addition, various cancer promoting and tumour causing chemicals are there which themselve cannot cause cancer but increase the incidences of tumour formation as they increase the cancer causing potential of previously present carcinogens. Various scientists from different parts of the world have worked earlier on the carcinogenic chemicals in diet and plants. A few studies to be mentioned here are that of Ames et al. (1990) on dietary pesticides; Gold et al. (1999) prepared a database on animal bioassay (CPDB); Gold et al. (1997) overviewed analyses of the carcinogenic potency database; Vainio & Wilbourn (1993) provided details on agents causally associated with human cancer; IARC (1997) published monographs on the evaluation of carcinogenic risk of chemicals to humans; Ames et al. (1987) ranked possible carcinogenic hazards; Matanoski et al. (1993) worked on cancer epidemiology among styrene-butadiene rubber workers; Hirono et al. (1978) on carcinogenic activity of *Symphytum officinale*, Russian scientists Culvenor et al. (1980) worked on toxicity of the alkaloids of Russian comfrey, a medicinal herb and item of human diet; Hirono et al. (1976) on carcinogenic activity of coltsfoot, *Tussilago farfara*; Herrmann (1978) reviewed nonessential constituents of vegetables, carrots, celery, parsnips, beets, spinach, lettuce, endives, chicory, rhubarb and artichokes; Hall et al. (1989) compared the carcinogenic risks of naturally occurring and adventitious substances in food; Toth & Erickson (1986) worked on cancer induction of mushroom; Matsumoto et al. (1991) also examined carcinogenicity of *Agaricus bisporus* in rats; Fazio et al. (1980) determined volatile *N*-nitrosamines in foodstuffs; Preussmann & Eisenbrand (1984) studied *N*-nitroso carcinogens in the environment; Carlson et al. (1987) studied glucosinolates in crucifer vegetables, broccoli, Brussels sprouts, cauliflower, collards, kale, mustard greens and kohlrabi; Chauhan et al.(1985) isolated carcinogenic N_2-[γ-*L*-(+)-glutamyl]-4-carboxyphenylhydrazine in the cultivated mushroom *Agaricus bisporus*; Tricker & Preussmann (1991) reported occurrence, formation, mechanisms and carcinogenic potential of *N*-nitrosamines in the diet; Beier et al. (1983) analysed linear furocoumarins (psoralens) in healthy celery *Apium graveolens*; Ivie et al. (1981) studied natural toxicants in human foods; Ko (1998) reported adulterants in Asian patent medicines; Bushway & Ponnampalam (1981) and Takagi et al. (1990) revealed α-chaconine and α-solanine content of potato products and their stability during several modes of cooking, Friedman & Dao (1990) studied distribution of glycoalkaloids in potato plants; Montgomery (1964) observed cyanide content and toxicity of tropical pulses; Eltayeb & Roddick (1984) studied changes in the alkaloid content of developing fruits of tomato (*Lycopersicon esculentum*); Pérez-Ilzarbe et al. (1990) studied phenolic compounds in apples; Winter & Herrmann (1986) studied esters and glucosides of hydroxycinnamic acids in vegetables; Pino et al. (1990) studied chemical and sensory properties of black pepper oil (*Piper nigrum*); Lee & Jaworski (1987) studied phenolic compounds in white grapes grown in New York; Keane et al. (1999) analysed Chinese herbal creams prescribed for dermatological conditions; and Ko (1998) studied adulterants in Asian patent medicines. However, until today there is hardly any such study has been reported from India.

CARCINOGENICITY OF NATURAL CHEMICALS

The public opinion regarding chemicals is that mostly they are only synthetic and all synthetic chemicals as toxic; however, every natural chemical is also toxic at some dose. Current cancer regulatory polices of America and other countries were based on the idea that rodent carcinogens are potential human carcinogens; however, the chemicals tested for carcinogenicity in rodents have been primarily synthetic. The enormous background of human exposures to natural chemicals, including medicinal herbs, has not been a focus of testing. Toxicological examination of synthetic chemicals, without similar examination of chemicals that occur naturally, has resulted in an imbalance in both data and perception about possible cancer hazards. The toxicology of synthetic and natural toxins is not fundamentally different. Medicinal herbs and dietary supplements, which are naturally occurring substances, have not been a focus of carcinogenicity testing despite the fact that they are often taken daily for long periods of time, and that the recommended doses are higher relative to toxicity than most other exposures (except pharmaceuticals and workplace exposures).

The vast proportion of chemicals to which humans are exposed, occur naturally. It was estimated that the daily average U.S. exposure to burn material in the diet is 2000 mg. The exposure to natural pesticides (the chemicals that plants produce to defend themselves) is 1500 mg; in comparison, the total daily exposure to all synthetic pesticide residues combined is 0.09 mg. Thus, 99.99% of the pesticides, which humans ingest are natural (Ames et al. 1990). Despite this enormously greater exposure to natural chemicals, among the chemicals tested for carcinogenicity in rats and mice, 76% (450/590) are synthetic (Gold et al. 1999).

The toxicology of natural and synthetic chemicals is almost similar, one expects and finds a similar positive rate for carcinogenicity among synthetic and natural chemicals. Since humans are exposed to so many more natural than synthetic chemicals (by weight and by number), humans are probably living in a sea of naturally occurring rodent carcinogens as defined by high dose rodent tests. It is probable that almost every fruit and vegetable in the market contains natural pesticides that are rodent carcinogens (acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline hydrochloride, benzaldehyde, benzyl acetate, caffeic acid, capsaicin, catechol, clivorine, coumarin, crotonaldehyde, 3,4-dihydrocoumarin, estragole, ethyl acrylate, N_2-γ-glutamyl-*p*-hydrazinobenzoic acid, hexanal methylformylhydrazine, *p*-hydrazinobenzoic hydrochloride, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, *d*-limonene, 3-methoxycatechol, 8-methoxypsoralen, *N*-methyl-*N*-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, 4-methylcatechol, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine etc. These natural chemicals show rodent carcinogenicity to some extent and occur in absinthe, allspice, anise, apple, apricot, banana, basil, beet, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate, cinnamon, cloves, coffee, collard greens, comfrey herb tea, corn, coriander, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mint, mushrooms, mustard, nutmeg, onion, orange, paprika, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric and turnip) (Gold & Slone 1999). These studies revealed that possible toxic hazards would be similar for natural or synthetic chemicals, just because a substance occurs naturally, that does not indicate that it will be safe.

HUMAN DEFENSE MECHANISMS AGAINST HERBAL CARCINOGENS

Humans have many natural defenses that buffer against normal exposures to toxins, and these defenses are usually non-specific. Thus, they work against both natural and synthetic chemicals. Examples of general defenses include the continuous shedding of cells exposed to toxins-the surface layers of the mouth, esophagus, stomach, intestine, colon, skin and lungs are discarded every few days; DNA repair enzymes, which repair DNA that has been damaged from many different sources; and detoxification enzymes of the liver and other organs which generally target classes of chemicals rather than individual chemicals. That human defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world; if a herbivore had defenses against only a set of specific toxins, it would be at a great disadvantage in obtaining new food when favored foods became scarce or evolved new chemical defenses (Ames et al. 1990).

Various natural toxins, which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates. Mold toxins, such as aflatoxin, has shown to cause cancer in rodents and other species including humans. Many of the common elements are carcinogenic to humans at high doses, e.g., salts of cadmium, beryllium, nickel, chromium and arsenic, despite their presence throughout evolution. Furthermore, epidemiological studies from various parts of the world show that certain natural chemicals in the diet can be carcinogenic to humans; for example, the chewing of betel nut with tobacco has been correlated with oral cancer and the mold toxin, aflatoxin, is carcinogenic to humans and many other species. Among the agents identified as human carcinogens by the International Agency for Research in Cancer (IARC), 61% occur naturally, 15 are natural chemicals, 11 are mixtures of natural chemicals, and five are infectious agents (Vainio & Wilbourn 1993, ICAR 1997).

Humans, who are the most recent creature of the evolution, have not had time to evolve a “toxic harmony” with all of their dietary and medicinal herbs. The human diet has changed markedly in the last few thousand years. Indeed, very few of the plants that humans eat today, e.g., coffee, cocoa, tea, potatoes, tomatoes, corn, avocados, mangoes, olives and kiwi fruit, would have been present in a hunter-gatherer’s diet. Natural selection works far too slowly for humans to have evolved specific resistance to the food toxins in these newly introduced plants and hybrid plants. For example, a recent case illustrates the potential hazards when a major grower introduced a new variety of highly insect-resistant celery into commerce, people who handled the celery developed rashes when they were subsequently exposed to sunlight. Some detective work found that the pest-resistant celery contained 6,200 parts per billion (ppb) of carcinogenic and mutagenic psoralens instead of the 800 ppb present in common celery (Ames et al. 1990).

RANKING POSSIBLE CANCER HAZARDS TO KNOWN RODENT CARCINOGENS

It is important to set priorities among possible cancer hazards by gaining perspective about the vast number of herbal chemicals to which humans are exposed. One reasonable strategy is to use a rough index to compare and rank possible carcinogenic hazards from a wide variety of chemical exposures at levels that humans typically receive, and then to focus on those that rank highest. If naturally occurring chemicals rank high in possible hazard compared to synthetic pollutants or food additives, then this is further evidence that chemicals are not safe just because they are natural. Although one cannot say whether the ranked chemical exposures are likely to be of major or minor importance in

human cancer, it is not prudent to focus attention on the possible hazards at the bottom of a ranking if, using the same methodology, there are numerous common human exposures with much greater possible hazards.

The HERP index (Human Exposure/Rodent Potency), which indicates what percentage of the rodent carcinogenic potency (TD_{50} in mg/kg/day) a human receives from a given daily lifetime exposure (mg/kg/day), of all rodent carcinogens in "carcinogenic potency database" for which average exposure information was available in the published literature, and it show that possible carcinogenic hazards (HERP values) for some historically high exposures in the workplace and some pharmaceuticals rank high, and that there is an enormous background of naturally occurring rodent carcinogens in typical portions of common foods that cast doubt on the relative importance of low-dose exposures to synthetic chemicals such as pesticide residues or synthetic food additives (Ames et al. 1987). As per the HERP ranking, the possible hazard for herbal remedies may be even relatively greater because mostly the pharmaceutical preparations are not used chronically, whereas the herbal remedies that are rodent carcinogens are recommended for chronic use.

Comfrey is a medicinal herb that is carcinogenic in rats. Formerly, it was recommended for well-being, but currently the PDR for Herbal Medicines indicates: "One should entirely forgo internal administration of the drug due to the presence, however small, of pyrrolizidine alkaloids which have hepatotoxic and carcinogenic effects. It has been determined that traces of the alkaloids present a danger" (Gruenwald et al. 1998). Poisoning epidemics by pyrrolizidine alkaloids have occurred in the developing world. In the U.S., poisonings including deaths, have been associated with use of herbal teas containing comfrey pyrrolizidine alkaloids reportedly reduce taurine, which is a hepatoprotective chemical; therefore, individuals who are low in taurine (e.g. vegetarians, since taurine is present in meat but absent in vegetables) may be at greater risk of poisoning from pyrrolizidine alkaloids (Huxtable 1995). Coltsfoot, which is a liver carcinogen in rats, has a HERP value for a cup of herbal tea of 0.9. The PDR for Herbal Medicines cautions that the pyrrolizidine alkaloids in flowers are possibly hepatotoxic and carcinogenic (Gruenwald et al. 1998).

RANKING POSSIBLE TOXIC HAZARDS OF HERBS AND DIETARY SUPPLEMENTS (NOT TESTED FOR CARCINOGENICITY)

An index, HERT, which is analogous to HERP, is the ratio of Human Exposure/Rodent Toxicity is used to rank possible toxic hazard of herbal medicine and dietary chemicals that have not been tested for carcinogenicity and may exhibit tumour-promoting properties. These promoters, while not causing cancer by themselves, may be viewed as subclass of co-carcinogens that interact with other factors to induce carcinomas (Heacker 1978). The HERT ranking indicates that herbs and dietary supplements rank high in possible toxic hazards when compared to food constituents that occur in high concentrations in common foods. Since supplements are often used chronically for long periods of time, by itself this indicates the importance for safety of a defined battery of toxicological testing. The HERT values for ginger, ginkgo, ginseng and garlic extracts range from 0.1 to 0.8, i.e. the recommended dose for humans (mg/kg/day) is from 0.1 to 0.8 percent of the lethal dose (mg/kg/day) in rodents. The HERT for valerian extract is 0.01. Some natural chemicals in foods also rank high in HERT, suggesting the importance of testing for carcinogenicity since HERT and HERP are highly correlated. Most of the high ranking plant chemicals in food and drug are natural pesticides and many have pharmacological effects, e.g. caffeine (a stimulant in coffee, tea, cola), trigonelline (in coffee), α-chaconine (a neurotoxin in potato), theobromine (in chocolate) and piperine (in black pepper).

Herbal medicines and dietary supplements are similar to pharmaceuticals in terms of ranking high in possible toxic hazard. This is expected since the pharmacologically active dose for both pharmaceuticals and herbal supplements is high relative to toxicity. Because the recommended dose is close to the toxic dose, and because about half of the natural chemicals are rodent carcinogens in standard animal cancer tests, it is likely that many dietary supplements from plants will be rodent carcinogens that would rank high in possible carcinogenic hazard (HERP) if they were tested for carcinogenicity. If the active chemical in the plant were identified and tested, it would likely have a high HERP value if it turned out to be a rodent carcinogen. It has been revealed in the publications from the "Carcinogenic Potency Project" that the HERT values for the synthetic chemicals in the diet would all rank below the HERT values for the herbs and dietary supplements.

ADVERSE EFFECTS OF HERBAL MEDICATIONS AND SUPPLEMENTS

The monitoring studies of herbal medications and herbal remedies indicate many toxic reactions, allergic reactions, drug interactions, adverse effects from the desired pharmacologic effect of the supplement, contamination and misidentification of the product or plant. Ernst (1998) has reported severe reactions to herbal products, including hepatitis, liver failure, anaphylactic shock and even death. Based on the ranking results in publications from the Carcinogenic Potency Project, adverse effects are not surprising; the recommended doses for herbal remedies are close to the toxic doses (mg/kg/day) in rodents. In this respect, the herbal dietary supplements resemble pharmaceutical drugs, and are in contrast to some highly regulated exposures to synthetic chemicals such as water pollutants, pesticide residues or food additives. Herbal products may have many beneficial effects, but their safety requires greater toxicological testing, including carcinogenicity testing. There is an absence of quantitative toxicological data on these products in the available published literature (Gold & Slone 1999).

CONCLUSION

As far as herbal medications are concerned hardly any toxicological data is available to assess their potential health hazards, despite the high doses recommended, the frequency with which herbals are taken chronically, and the fact that consumers are self-medicating with these products. In order to protect consumers from potentially harmful, long-term effects of herbal medicines, a defined series of toxicological testing is required for evaluation of safety, and a Regulatory Board scrutiny is needed because of the lack of information on possible herbal drug interactions and the evidence that mostly these products are not standardised, have been adulterated, and can contain synthetic pharmaceuticals or high levels of heavy metals. As like synthetic pharmaceuticals, herbal drugs are not being tested for carcinogenicity may be rank high in possible toxic hazard. Gaining a broad perspective about the herbal medications, which human beings consume, is important when setting research and regulatory priorities for such drugs and should include the toxic dose level of a given herb or herbal product.

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