Phytochemicals – biomolecules for prevention and treatment of human diseases-a review

Manas Kumar Mukhopadhyay; Pratyusha Banerjee and Debjani Nath*

Department of Zoology, University of Kalyani, Nadia,West Bengal, India

*** Corresponding author**

Email Address: nath_debjani@yahoo.co.in

Abstract:

Ayurveda is the most ancient healthcare system describes thousands of medicinal plants with their medicinal properties. In recent times, developed countries are turning to the use of traditional medicinal systems because the phytochemicals are potent in different therapeutic applications as they show defensive mechanism of action against a number of chronic diseases including cancer, cardiovascular disease, diabetes, neurodegenerative disease. Plant biomolecules are also involved in anti viral as well as antimicrobial activity and also show efficacy in radioprotection. But still there are some difficulties in proper therapeutic administration of phytochemicals due to their low water solubility, low absorptivity and bioavailability. So a strategy of engineered phytochemicals has been developed to enhance solubility, cellular permeability, proteolytic stability and half-life of plant biomolecules. Still further research is required to ensure high yield as well as viability and bioavailibity of the plant biomolecules in different therapeutic application.

Key words: Medicinal plants and herbs, Plant biomolecules, Therapeutic application, Engineered phytochemicals.

1. Introduction:

Ayurveda is the most ancient health care system and is practiced widely in India, Srilanka and other countries. Atharvveda (around 1200 BC), Charak Samhita and Sushrut Samhita (100 - 500 BC) are the main classics that given detailed descriptions of over 700 herbs. In 78 A.D Dioscorides wrote “De Materia Medica”, describing thousands of medicinal plants. This treatise included descriptions of many medicinal plants that remain important in modern medicine, not because they continue to be used as crude drug preparations, but because they serve as the source of important pure chemicals that have important use in modern therapy. The physicians of today continue to use many substances and products derived from natural sources, usually for the same therapeutic benefit as the crude drug. These single chemical entities, i.e., drugs, form the basis for much of our

ability to control disease. In recent times, there have been increased waves of interest in the field of research in chemistry of natural Products. This level of interest can be attributed to several factors, including unmet therapeutic needs, the remarkable diversity of both chemical structure and biological activities of naturally occurring secondary metabolites, the utility of novel bioactive natural products as biochemical probes, the development of novel and sensitive techniques to detect biologically active natural products, improved techniques to isolate, purify, and structurally characterize these active constituents, in solving the demand for supply of complex natural products. The R & D thrust is focused on development of new innovative/indigenous plant based drugs from the traditional system of medicine. The World Health Organization has also recognized the importance of traditional medicine and has created strategies, guidelines and standards for botanical medicines. Over the past decade, there has been a resurgence of interest in the investigation of natural materials as a source of potential drug substance. This article is aimed at highlighting the invaluable role of plant biomolecules in different therapeutic applications.

2. Importance of phytochemicals:

In recent times, developed countries are turning to the use of traditional medicinal systems that involve the use of herbal drugs and remedies and according to the World Health Organization (WHO), almost 65% of the world's population has incorporated the value of plants as a methodology of medicinal agents into their primary modality of health care. It is often noted that 25% of all drugs prescribed today come from plants. This estimate suggests that plant-derived biomolecules make up a significant segment of natural product– based pharmaceuticals. Out of many families of secondary metabolites, nitrogen-containing alkaloids have contributed the largest number of drugs ,ranging in effects from anticholinergics (atropine) to analgesics (opium alkaloids) and from antiparasitics (quinine) to anticholinesterases (galantamine) to antineoplastics (vinblastine/vincristine), terpenoids (including steroids) have made an equally important contribution to human health. They range from Na+/K+ pump-inhibiting cardiac glycosides from *Digitalis* spp., to antineoplastic paclitaxel , antimalarial artemisinin, anti-inflammatory triptolide. The goals of using plants as sources of therapeutic agents are, *a*) to isolate bioactive compounds for direct use as drugs, e.g., digoxin, digitoxin, morphine, reserpine, taxol, vinblastine, vincristine; *b*) to produce bioactive compounds of novel or known structures as lead compounds for semisynthesis to produce patentable entities of higher activity and/or lower toxicity, e.g., metformin, nabilone, oxycodon (and other narcotic analgesics), taxotere, teniposide, verapamil, and amiodarone, which are based, respectively, on galegine, morphine, taxol, podophyllotoxin, khellin, and khellin; *c*) to use agents as pharmacologic tools, e.g., lysergic acid diethylamide, mescaline, yohimbine; and *d*) to use the whole plant or

part of it as a herbal remedy, e.g., cranberry, echinacea, feverfew, garlic, ginkgo biloba, St. John's wort, saw palmetto.

Table1. Numbers of medicinal species documented in different countries and regions:

Country	Total no. of native species	No. of medicinal species	Reference
Bulgaria	3567	750	[1]
France	4630	900	[1]
Hungary	2214	270	[1]
Korea	2898	1000	[1]
Malaysia	15500	1200	[1]
Nepal	6973	900	[1]
Pakistan	4950	1500	[1]
Phillipines	8931	850	[1]
Srilanka	3314	550	[1]
Thailand	11625	1800	[1]
Vietnam	10500	1800	[1]
Chile	4672	469	[2]
China	27100	11146	[3]
India	17000	7500	[4]
Mexico	30000	2237	[5]
United states	20000	2572	[6]
South Africa	22000	4000	[7]

Table2. Indian medicinal plants and their medicinal property:

Common Name	Scientific Name	Uses
Acacia	*Acacia greggi*	astringent, demulcent, emollient
Agrimony	*Agrimonia eupatoria*	blood coagulant

Pimenta	*Pimenta dioica*	heals wounds, bruises
Ajwain	*Trachyspermum ammi*	antibacterial, carminative, digestive
Ashok	*Saraca asoca*	relieves menstrual pain, diabetes, uterine disorders
Amla	*Phyllanthus emblica*	Cough, diabetes, laxative, acidity
Ashwagandha	*Withania somnifera*	relieves stress, nerve disorder, restores normal function of body
Brahmi	*Bacopa monnieri*	jaundice, anemia, dropsy
Bael	*Aegle marmelos*	constipation, diarrhea, dysentery
Chirata	*Swertia chirata*	burn, skin diseases, fever
Guggul	*Commiphora wightii*	asthma, hydrocele, diabetes
Guluchi	*Tinospora cordifolia*	jaundice, gout, piles, fever
Kalmegh	*Andrographis paniculata*	gastritis, fever, weakness
Makoi	*Solanum nigrum*	dysentery, diuretic, debility
Pashan Bheda	*Coleus barbatus*	calculus, stones in kidney
Sarpa Gandha	*Ranwolfia serpentina*	insomnia, hypertension
Tulsi	*Ocimum tenuiflorum*	expectorant, cough, cold
Vai Vidanka	*Embelia ribes*	skin disease, helminthiasis
Peppermint	*Mentha piperita*	pain-killer, digestive
Vringraj	*Eclipta alba*	anti-inflammatory, leukemia, stress reliever
Chitrak	*Plumbargo zeylanica*	dyspepsia, inflammation, cough, colic
Harada	*Terminalia chebula*	leprosy, inflammation, vomiting, insomnia
Neem	*Azadirachta indica*	analgesic, astringent, epilepsy
Kantakari	*Solanum xanthocarpum*	appetizer, stomach ache, diuretic

Table 3. Indian medicinal herbs and their property:

Common name	Scientific name	Uses
Lemon Balm	*Melissa officinalis*	digestion, stomach spasms, anti-viral
Angelica	*Angelica sylvestris*	gastritis, cramps, digestion
Chickweed	*Stellaria media*	itching, irritation, rashes
Cleavers	*Galium aparine*	skin diseases, diuretic
Couch grass	*Cynodon dactylon*	rheumatism, cystitis, gout
Dandelion	*Taraxacum officinale*	dissolves kidney and gallstones, diuretics
Elderberry	*Sambucus canadensis*	bronchitis, cold, cough
Garlic	*Allium sativum*	anti-microbial, cardiovascular treatment
Ginger	*Zingiber officinale*	motion sickness, vomiting, flatulence, diarrhea
Lavender	*Lavandula angustifolia*	stress reliever, boosts spirits, stomach disorders
Red Clover	*Trifolium pratense*	rejuvenatory, skin nourishing
Rosemary	*Rosmarinus officinalis*	improves blood supply to brain
Thyme	*Thymus pulegioides*	antifungal, anti-bacterial, expectorant
Yarrow	*Achillea millefolium*	wound cleansing, blood coagulation, digestive

3. List of phytochemical based therapeutic approaches:

Table 4: Phytochemicals and their chemopreventive activity:

Binding phytochemical	**Molecular targets**	**Chemopreventive effect**	**Refferences**
3′,4′,7-trihydroxyisoflavone	PI3 K Cyclin-dependent kinase 2	EGF-induced cell proliferation and transformaion	[8]
5-deoxykaempferol	SRC Ribosomal S6 kinase2 (RSK) PI3K	UVB-induced two-stage skin carcinogenesis UVB-induced COX2 and VEGF expression	[9]
6-gingerol	Leukotriene A_4 hydrolase (LTA$_4$H)	Xenograft tumour volume of human HCT116 colon cancer cells	[10]
Caffeic acid	FYN	UVB-induced COX2 expression	[11]
Cyanidin	RAF Mitogen-activated protein kinase kinase 4 (MKK4) MEK1	UVB-induced COX2 expression	[12]
Cryptotanshinone	Signal transducer and activator of transcription3	Human prostate cancer cell proliferation	[13]
Deguelin	Heat shock protein 90	Xenograft tumour volume of	[14]

		human lung, head, neck, stomach and prostate cancer cells	
Delphinidin	FYN RAF,MEK1,ERKs ,MKK4 PI3K	TNFα-induced COX2 expression TPA-induced cell transformation UVB-induced COX2 expression	[15] [16][17]
(-)-Epigallocatechin gallate	FYN Insulin-like growth factor-1 receptor Glucose-regulated protein 78 Heat shock protein 90 ζ-chain-associated protein kinase70 Ras GTPase activating protein SH3 domain binding protein1	EGF-induced cell transformation Cell proliferation and transformation Etoposide-induced breast cancer cell death and drug resistance TCDD-mediated gene induction in hepatoma cells Leukaemia proliferation Anchorage-independent growth of human and mouse lung cancer cell lines	[18] [19] [20] [21] [22] [23]
Equol	MEK1	TPA-induced cell transformation	[24]
Fisetin	CDK6	Kinase activity	[25]
Kaempferol	SRC	UVB-induced two stage skin	[26]

		carcinogenesis	
	RSK2	RSK2-mediated cancer cell proliferation	[27]
	PI3K	EGF-induced cell transformation	[28]
Luteolin	SRC Protein kinase Cε	UVB-induced two-stage skin carcinogenesis	[29]
Myricetin	FYN	UVB-induced two-stage skin carcinogenesis	[30]
	RAF	UVB-induced MMP9 activity and expression	[31]
	MKK4	TNFα-induced VEGF expression	[32]
	MEK1	TPA- or EGF-induced cell tranformation	[33]
	PI3K	UVB-induced angiogenesis	[34]
	Janus kinase 1	Cell transformation	[35]
Procyanidin B2	MEK1	TPA-induced cell transformation	[36]
Quercetin	RAF	TPA-induced cell transformation	[37]
	MEK1	TNFα-induced MMP9 activation	[38]
	PI3K	Arsenite-induced COX2 expression	[39]

Resveratrol	COX2 LTA4H	Human colon cancer cell proliferation Xenograft tumour volume of human pancreatic cancer cells	[40] [41],[42]
In other diseases			
Active phytochemicals	**Target site**	**Biological effect**	**References**
Ajoene	ROS mediated apoptosis	Leukemic cells Adipocyte	[43][44]
Chlorogenic acid and saponins	S-Glut-1mediated transport	Intestinal glucose transport	[45]
Esters of triterpene alcohols from rice bran oils	HMG Co-A reductase	hepatic cholesterol esterase and tocotrienols	[46]

Table.5 plants and their antiviral activity:

Plant tested	Minimum Antiviral Activity (Ag/mb)		
	Herpes simplex	Sindbis	Polio
Asteraceae *Conyza aegyptiaca (L.)* Aiton	500	250	500
Bombacaceae *Adansonia digirara L* (root-bark)	125	250 250	250

(leaves)	<62.5		
Commelinaceae *Palisora hirsuta* (Thunb.) K. Schum.	<62.5	500	250
Davalliaceae *Davallia chaerophyUoides* (Poir.) Steud.	500	-	-
Malvacae *Sida acuta* Burm. f.	250	-	-
Moraceae *Ficus ovata* Vahl	125	-	250
Rubiaceae *Mitracarpus villosus (Sw.) DC.*	125	-	500
Rutaceae *Zanthorvlunt zanthoxvloides* (Lam.) Zepernick & Tiniler	500	-	-
Simarubaceae *Harrisonia abyssinica Oliv*	250	-	-
Sapindaceae *Paullinia pinnata* L.	125	-	-

Table.6. phytochemicls and their antimicrobial activity:

Common name	Scientific name	Compound	Class	Activity	Relative toxicity
Alfalfa	*Medicago*	?	?	Gram-positive	2.3

	sativa			organisms	
Allspice	*Pimenta dioica*	Eugenol	Essential oil	General	2.5
Aloe	*Aloe barbadensis, Aloe vera*	Latex	Complex mixture	*Corynebacterium, Salmonella,Streptococcus, S. aureus*	2.7
Apple	*Malus sylvestris*	Phloretin	Flavonoid derivative	General	3.0
Ashwagandha	*Withania somniferum*	Withafarin A	Lactone	Bacteria, fungi	0.0
Bael tree	*Aegle marmelos*	Essential oil	Terpenoid	Fungi	?
Basil	*Ocimum basilicum*	Essential oils	Terpenoids	*Salmonella*, bacteria	2.5
Bay	*Laurus nobilis*	Essential oils	Terpenoids	Bacteria, fungi	0.7
Betel pepper	*Piper betel*	Catechols, eugenol	Essential oils	General	1.0
Black pepper	*Piper nigrum*	Piperine	Alkaloid	Fungi, *Lactobacillus, Micrococcus, E. coli, E. faecalis*	1.0
Blueberry	*Vaccinium* sp p.	Fructose	Monosaccharide	*E. coli*	?
Brazilian pepper tree	*Schinus terebinthifolius*	Terebinthone	Terpenoids	General	1.0

Buchu	*Barosma setulina*	Essential oil	Terpenoid	General	2.0
Burdock	*Arctium lappa*	?	Polyacetylene, tannins, terpenoids	Bacteria, fungi, viruses	2.3
Buttercup	*Ranunculus bulbosus*	Protoanemonin	Lactone	General	2.0
Caraway	*Carum carvi*	?	Coumarins	Bacteria, fungi, viruses	?
Cascara sagrada	*Rhamnus purshiana*	Tannins	Polyphenols	Viruses, bacteria, fungi	1.0
Cashew	*Anacardium pulsatilla*	Salicylic acids	Polyphenols	*P. acnes*	?
Ceylon cinnamon	*Cinnamomum verum*	Essential oils, others	Terpenoids, tannins	General	2.0
Chamomile	*Matricaria chamomilla*	Anthemic acid	Phenolic acid	*M.tuberculosis*, *S. typhimurium*, *S. aureus*, helminths	2.3
Chapparal	*Larrea tridentata*	Nordihydroguaiaretic acid	Lignan	Skin bacteria	2.0
Chili peppers, paprika	*Capsicum annuum*	Capsaicin	Terpenoid	Bacteria	2.0
Clove	*Syzygium aromaticum*	Eugenol	Terpenoid	General	1.7

Coca	*Erythroxylum coca*	Cocaine	Alkaloid	Gram-negative and -positive cocci	0.5
Cranberry	*Vaccinium* spp.	Fructose	Monosaccharide	Bacteria	?
Dill	*Anethum graveolens*	Essential oil	Terpenoid	Bacteria	3.0
Eucalyptus	*Eucalyptus globulus*	Tannin	Polyphenol	Bacteria, viruses	1.5
Fava bean	*Vicia faba*	Fabatin	Thionin	Bacteria	?
Gamboge	*Garcinia hanburyi*	?	Resin	General	0.5
Garlic	*Allium sativum*	Allicin, ajoene	Sulfoxide	General	?
Ginseng	*Panax notoginseng*	?	Saponins	*E. coli*, *Sporothrix schenckii*,*Staphylococcus*, *Trichophyton*	2.7
Glory lily	*Gloriosa superba*	Colchicine	Alkaloid	General	0.0
Goldenseal	*Hydrastis canadensis*	Berberine, hydrastine	Alkaloids	Bacteria, *Giardia duodenale*, trypanosomes	2.0
Gotu kola	*Centella asiatica*	Asiatocoside	Terpenoid	*M. leprae*	1.7
Grapefruit peel	*Citrus paradisa*	?	Terpenoid	Fungi	?

Green tea	*Camellia sinensis*	Catechin	Flavonoid	General	2.0
Hemp	*Cannabis sativa*	β-Resercyclic acid	Organic acid	Bacteria and viruses	1.0
Henna	*Lawsonia inermis*	Gallic acid	Phenolic	*S. aureus*	1.5
Lemon balm	*Melissa officinalis*	Tannins	Polyphenols	Viruses	?
Lemon verbena	*Aloysia triphylla*	Essential oil	Terpenoid	*Ascaris*	1.5
Licorice	*Glycyrrhiza glabra*	Glabrol	Phenolic alcohol	*S. aureus, M. tuberculosis*	2.0
Lucky nut, yellow	*Thevetia peruviana*	?	?	*Plasmodium*	0.0
Marigold	*Calendula officinalis*	?	?	Bacteria	2.7
Mountain tobacco	*Arnica montana*	Helanins	Lactones	General	2.0
Oak	*Quercus rubra*	Tannins	Polyphenols	?	?
Olive oil	*Olea europaea*	Hexanal	Aldehyde	General	?
Onion	*Allium cepa*	Allicin	Sulfoxide	Bacteria, *Candida*	?
Orange peel	*Citrus sinensis*	?	Terpenoid	Fungi	?

Oregon grape	*Mahonia aquifolia*	Berberine	Alkaloid	*Plasmodium*	2.0
Pao d'arco	*Tabebuia*	Sesquiterpenes	Terpenoids	Fungi	1.0
Pasque-flower	*Anemone pulsatilla*	Anemonins	Lactone	Bacteria	0.5
Peppermint	*Mentha piperita*	Menthol	Terpenoid	General	?
Periwinkle	*Vinca minor*	Reserpine	Alkaloid	General	1.5
Poinsettia	*Euphorbia pulcherrima*	?	?	General	0.0
Poppy	*Papaver somniferum*	Opium	Alkaloids and others	General	0.5
Potato	*Solanum tuberosum*	?	?	Bacteria, fungi	2.0
Purple prairie clover	*Petalostemum*	Petalostemumol	Flavonol	Bacteria, fungi	?
Quinine	*Cinchona* sp.	Quinine	Alkaloid	*Plasmodium* spp.	2.0
Rauvolfia, Chandra	*Rauvolfia serpentina*	Reserpine	Alkaloid	General	1.0
Rosemary	*Rosmarinus officinalis*	Essential oil	Terpenoid	General	2.3
Sainfoin	*Onobrychis viciifolia*	Tannins	Polyphenols	Ruminal bacteria	?
Sassafras	*Sassafras*	?	?	Helminths	2.0

	albidum				
Savory	*Satureja montana*	Carvacrol	Terpenoid	General	2.0
Senna	*Cassia angustifolia*	Rhein	Anthraquinone	*S. aureus*	2.0
Snakeplant	*Rivea corymbosa*	?		General	1.0
St. John's wort	*Hypericum perforatum*	Hypericin, others	Anthraquinone	General	1.7
Sweet flag, calamus	*Acorus calamus*	?	?	Enteric bacteria	0.7
Tansy	*Tanacetum vulgare*	Essential oils	Terpenoid	Helminths, bacteria	2.0
Tarragon	*Artemisia dracunculus*	Caffeic acids, tannins	Terpenoid	Viruses, helminths	2.5
Thyme	*Thymus vulgaris*	Caffeic acid	Terpenoid	Viruses, bacteria, fungi	2.5
Tree bard	*Podocarpus nagi*	Totarol	Flavonol	*P. acnes*, other gram-positive bacteria	?
Valerian	*Valeriana officinalis*	Essential oil	Terpenoid	General	2.7
Willow	*Salix alba*	Salicin	Phenolic glucoside	?	?
Wintergreen	*Gaultheria procumbens*	Tannins	Polyphenols	General	1.0

Woodruff	*Galium odoratum*	?	Coumarin	General	3.0
Yarrow	*Achillea millefolium*	?	?	Viruses, helminths	2.3

Table 7.Phytochemicals with their radioprotective activity:

Plants with family	Radioprotective efficacy	References
Aegle marmelos Rutaceae	To promote digestion, treat colic, diarrhoea and dysentery, intermittent fever, melancholia and heart palpitation. A. marmelos provided protection against radiation-induced sickness and mortality in mice.	[47]
Acanthopanax senticosus Araliaceae	To restore normal functioning of spleen and kidneys. Also used as a remedy for bronchitis, heart ailments and rheumatism Pre-irradiation administration of Shigoka extract rendered maximum survival (80%), while post-irradiation administration exhibited 30% survival.	[48]

Ageratum conyzoides L. Asteraceae	In India A. conyzoides leaves are applied to cuts and sores, while the juice is considered as antilithic. An alcoholic extract of A. conyzoides shoe efficacy inastrointestinal and bone marrow related death .	[49]
Allium cepa L Alliaceae	.Administration of the dried bulb of Allium cepa was active against x-irradiation.	[50]
Allium sativum L. Gaertn Alliaceae	Radioprotective efficacy of aged garlic extract (containing compounds such as S-allylcysteine, S-allylmercaptocysteine, allixin and selenium which are stable, highly bioavailable and possess significant antioxidant and anticarcinogenic)has been reported.	[51]
Aloe arborescens Liliaceae	Acts as a cell proliferant, healer, demucent and allergy reducer. Topically it is used for skin ulcers, burns, irritations and bites An extract of Aloe arborescens provided protection to mouse skin against soft x-irradiation by scavenging hydroxyl radicals and reducing alterations in enzyme activity.	[52]
Archangelica officinalis Hoffm.Umbelliferae	Administration of a combination of Archangelica officinalis and Ledum palustre extracts before irradiation rendered 70% survival.	[53]
Angelica sinensis (Oliver) Diels Apiaceae	The polysaccharide fraction, containing a ferulic acid, of Angelica sinensis increased survival in irradiated mice by promoting haemopoietic stem cell proliferation.	[54]
Curcuma longa Linn. Zingiberaceae	Pharmacological activities include antiinflammatory, anti-HIV, antibacteria, antitumour, antioxidant and nematocidal effects. Curcumin (diferuloylmethane) has been reported to render radioprotective effect.	[55]

Ginko biloba Linn. Cycadaceae	Ethanolic extract of dried leaves reported to be effective on clastogenic factors from plasma of human subjects exposed to irradiation and on rat cerebellar neuronal cell culture against hydroxyl radical induced apoptosis.	[56,57]
Hypericum perforatum Linn. Hypericaceae	Hypericum perforatum aqueous extract protected bone marrow and intestinal mucosa against x-ray in a concentration and time-dependent manner.	[58-61]
Lycium chinense Solanaceae	Administration of root extract prior to x-irradiation significantly improved the recovery of leukocyte, erythrocyte and thrombocyte counts and haematocrit.	[62]
Mentha arvensis Linn. Lamiaceae	It has carminative, antiseptic, refrigerant, stimulant, emmenagogue and diuretic properties .Pre-irradiation treatment with chloroform extract protected mice against gastrointestinal and bone marrow death .	[63]
Moringa oleifera Lam. Moringaceae	M. oleifera is used in Ayurveda to treat asthma, gout, rheumatism, inflammation, epilepsy, cardiac and circulatory disorders, nervous debility and healing of wounds. Pre-treatment with a leaf extract significantly reduced the percent of aberrant cells in metaphase chromosomes to normal range by day 7 post-irradiation in mice.	[64]
Piper longum Linn. Piperaeae	The ethanolic extract was found to protect mice against the radiation induced decline in WBC, bone marrow cells a-esterase positive cells and GSH.	[65]
Syzygium cumini L. Skeels Myrtaceae	In Ayurveda, S. cumini is used to treat bronchitis, asthma, dyspepsia, diabetes, ulcers and blood impurities. Treatment of human peripheral blood lymphocytes with S. cumini leaf extract before γ-radiation significantly reduced	[66]

		micronuclei-induction.	
4.	Tephrosia purpurea (L.) Pers. Fabaceae	T. purpurea roots are used to treat snake bite; diarrhoea, liver and spleen disorders, inflammation, boils and pimples. Tephrosia extract protected Swiss albino mice against radiation induced haemopoietic injury.	[67]

Potential therapeutic applications of phytochemicals:

4.1. Therapeutic application in cancer:

Several proteins have been identified as specific targets of some phytochemicals (TABLE 4). Representative signalling pathways targeted by various phytochemicals include the MAPK pathways, the oncogenic AKT pathway and proteins involved in cell cycle progression [12,17,24,32].

4.1.1 Interfering with the MAPK signaling pathways:

MEK1 is an important downstream component of oncogenic RAS signalling and potentially a good target for disrupting MAPK signalling. The development of pharmacological inhibitors of MEK1, such as PD [37] [29], has shown that MEK1 possesses a unique binding pocket adjacent to its ATP-binding site,and computer modelling has indicated that several phytochemicals, including quercetin[37], myricetin[33] and equol[24], could dock with this allosteric pocket. An analogue of resveratrol (RSvL2) was shown to strongly bind MEK1. The mechanism of allosteric inhibition of MEK is attributed to the inhibitor being able to stabilize the inactive conformation of the activation loop and deform the catalytic site.

4.1.2 Suppressing AKT signaling*:*

AKT and mTOR mainly reprogramme metabolic pathways in cancer cells, it is also thought to be involved in pathways that control the availability of nutrients acting through AMP activated protein kinase (AMPK), which controls glucose and lipid metabolism by sensing changes in nutrient and extracellular energy levels. This suggests that the AKT-mediated oncogenic pathway could be regulated by nutrients. PI3K is an upstream regulator of AKT–mTOR signalling and also interacts with several phytochemicals. Based on X-ray crystallography, quercetin and myricetin have been shown to directly bind and suppress PI3K activity [39,45].

4.1.3 Intervening with cell cycle progression:

Regulating cancer cell proliferation is crucial for chemoprevention. Cyclin-dependent kinases (CDKs), the essential proteins for cell cycle progression, bind with cyclins to form CDK–cyclin complexes [68]. Many CDK inhibitors (CDKIs), such as the p21 and p27 proteins, attenuate formation of these complexes and block cell cycle progression [19]. Several phytochemicals can function as CDKIs. Such as metabolite of the soybean isoflavone daidzein, is a direct inhibitor of CDK2 and CDK4 [51].

4.2. Therapeutic application in Diabetes:

Tea and several plant polyphenols were reported to inhibit a-amylase and sucrase activity, decreasing postprandial glycemia[69]. Individual polyphenols, such as β-catechin,epicatechin [70] ,epigallocatechin, epicatechin gallate, isoflavones from soyabeans, tannic acid, glycyrrhizin from licorice root, chlorogenic acid and saponins also decrease S-Glut-1 mediated intestinal transport of glucose [45]. Saponins delay the transfer of glucose from stomach to the small intestine.The water-soluble dietary fibres, guar gum, pectins and polysaccharides slow the rate of gastric emptying and thus absorption of glucose. The α-glucosidase inhibitors (acarbose and the others) are presently recommended for the treatment of obesity and diabetes. Phytochemicals have been shown to demonstrate such activity [71]. Plant phenols induce vasorelaxation by the induction of endothelial nitric oxide synthesis or increased bioavailability and the NO-cGMP pathway [30, 29].

4.3. Therapeutic application in Cardiovascular Disease:

The link between flavonoids and atherosclerosis is based partly on the evidence that some flavonoids possess antioxidant properties and have been shown to be potent inhibitors of LDL oxidation in vitro. For example, the phenolic substances in red wine inhibit oxidation of human LDL [40]. Flavonoids have also been shown to inhibit platelet aggregation and adhesion [72] which may be another way they lower the risk of heart disease. Isoflavones in soy foods have been reported to lower plasma cholesterol and also to have estrogenlike effects [73]. Garlic oil or garlic has been shown to be hypolipidemic in humans, with a recent meta-analysis suggesting that one half clove of garlic per day lowered serum cholesterol by approximately 9%.[74]. The same amount of garlic was shown to reduce cholesterol levels and severity of atherosclerosis in cholesterol-fed rabbits. Garlic contains a number of compounds, but those thought to be the most active are diallyl disulfide and its mono S oxide (allicim). The mechanism of hypercholesterolemia may be the inhibition of cholesterol synthesis [19].

4.4. Therapeutic application in neurodegenerative diseases:

As is the case with major diseases of other organ systems (cardiovascular disease, diabetes and cancers), data from epidemiological studies of human populations suggest that phytochemicals in fruits and vegetables can protect the nervous system against disease. For example, phytochemicals reduced risk for Alzheimer's disease [75].Because of their beneficial effects on the cerebral vasculature, phytochemicals may also reduce the risk of stroke [76] .Dietary supplementation with blueberries protected dopaminergic neurons against dysfunction and degeneration in a rat model of Parkinson's disease [77], improved learning and memory without affecting amyloid pathology in a mouse model of Alzheimer's disease[78] and reduced brain damage and improved functional outcome in a rat model of stroke [79].Apple juice concentrate prevented age-related impairment of cognitive function in mice [80]. Moderate consumption of red wine reduced amyloid pathology in a mouse model of Alzheimer's disease [81].Considerable effort has been aimed at identifying specific molecules responsible for the health benefits conferred by plants. Four different phytochemicals (sulforaphane, resveratrol, curcumin and the cannabinoid THC) which considerable evidence suggests have neuroprotective properties that likely involve a hormetic mechanism of action.

5. Challenges of phytochemical therapy:

Despite the benefits, many phytochemicals have poor water solubility, low absorptivity and bioavailability. The intended therapeutic role of ingested phytochemicals might be different than their *in vivo* activity once the food matrix is disrupted [46] due to variation in their metabolism and disposition [Fig 1].

5.1 Sources of variation in phytochemical metabolism and disposition

Researchers investigation on the pharmacokinetics of phytochemicals in humans have shown substantial variation .Circulating concentrations of phytochemicals, such as psoralens, lignans, and the flavonoids naringenin and hesperitin, can vary widely among individuals [46, 82]. The process of phytochemical disposition, like that of disposition of drugs and other xenobiotics, involves absorption, metabolism, distribution, and excretion, and each of these parts may contribute to pharmacokinetic variability.

5.1.1 Phytochemical metabolism by gut bacteria

Gut bacteria can hydrolyze glycosides, glucuronides, sulfates, amides and esters [82]. They also carry out reduction, ring-cleavage, demethylation and dehydroxylation reactions.The hydrolysis of glycosides and glucuronides typically results in metabolites that are more biologically active than the parent compounds. In contrast, further bacterial degradation and transformation of aglycones can lead to production of more or less active compounds, depending on the substrate being metabolized and the products formed. Plant polyphenols,

including phytoestrogens such as the isoflavones and lignans, are extensively metabolized in the gut by intestinal bacteria.

5.1.2 Phytochemical metabolism by polymorphic phase II conjugating enzymes

Phytochemicals are metabolized *in vivo* by biotransformation enzymes in a manner similar to that of other xenobiotics. Many classes of phytochemicals are rapidly conjugated with glutathione, glucuronide, and sulfate moieties and excreted in urine and bile. Thus, in theory, polymorphisms in biotransformation enzymes, such as the glutathione *S*-transferases (GST), UGT, and SULT, have the capacity to affect phytochemical metabolism in the same fashion as they do carcinogens and other xenobiotics

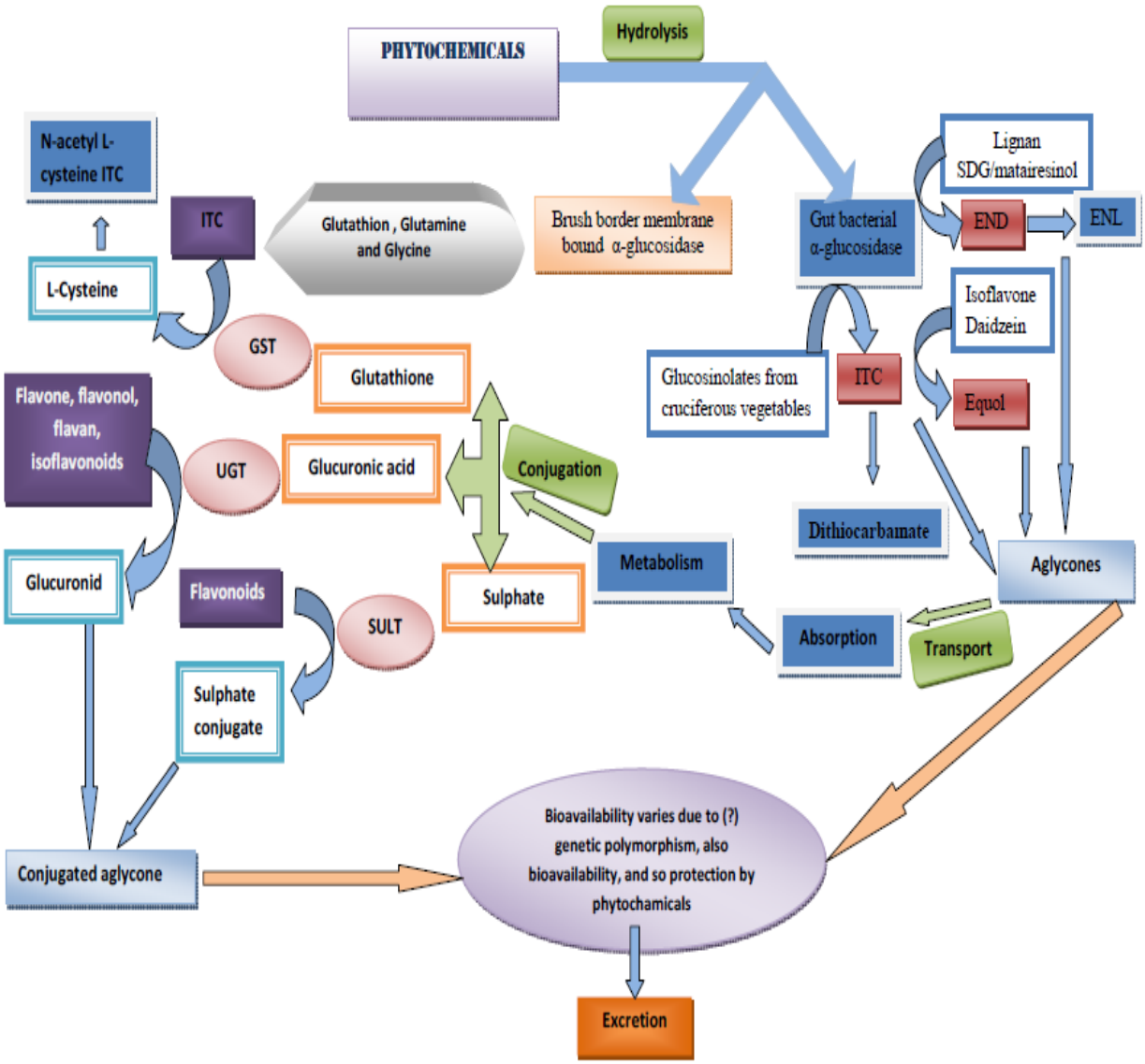

Figure 1: Schematic diagram presenting sources of variation in phytochemical metabolism and disposition.

6. Approaches in engineering phytochemicals for conjugation:

Novel antioxidant loaded drug delivery systems such as polymeric nanoparticles have been identified as alternatives that should provide longterm delivery at the therapeutic level, prevent antioxidant degradation, and increase pharmacological activity of such antioxidants [82].

6.1. Delivery of phytochemical thymoquinone using molecular micelle modified poly(D, L lactide*co*-glycolide) (PLGA) nanoparticles:

Thymoquinone (TQ) is a quinone-based phytochemical present in *Nigella sativa (Ranunculaceae)* black seed oil is a powerful antioxidant and anticancer drug, but its administration is limited due to poor water solubility .In addition, administration of high dosages to rats has resulted in hypoactivity and difficulty in respiration associated with reduced glutathione in the liver and kidney [41]. Another report has shown that TQ was capable of reducing blood glucose levels and inducing allergic dermatitis [83]. To overcome these disadvantages, biodegradable and biocompatible polymeric nanoparticles would be attractive alternatives for TQ delivery as it provides improved TQ solubility, controlled delivery, and enhanced therapeutic properties.

6.2. Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin") for human cancer therapy:

Though curcumin have widespread clinical application in cancer and other diseases, it has limited activity due to poor aqueous solubility, and consequently, minimal systemic bioavailability. Nanoparticle-based drug delivery approaches have the potential for rendering hydrophobic agents like curcumin dispersible in aqueous media. Polymeric nanoparticle encapsulated formulation of curcumin – nanocurcumin have been synthesized – utilizing the micellar aggregates of cross-linked and random copolymers of N-isopropylacrylamide (NIPAAM), with N-vinyl-2-pyrrolidone (VP) and poly (ethyleneglycol)monoacrylate (PEG-A). Nanocurcumin, unlike free curcumin, is readily dispersed in aqueous media and show therapeutic efficacy to free curcumin against a panel of human pancreatic cancer cell lines [84].

Discussion and Conclusion:

Phytochemicals are potentially involved as protective compounds for a number of chronic diseases. Reactive oxygen species (ROS) or oxidants formed in our body due to exogenous and endogenous factors are found to be responsible for many diseases such as cancer, cardiovascular disease, neurodegenerative diseases, inflammatory disease, ischemia-reperfusion injury and aging. The phytochemicals have the ability to neutralize the free radicals or reactive oxygen species or oxidants responsible for the onset of the diseases. The mechanisms by which the plant biomolecules provide defense against ROS mediated diseases are ROS scavenging, reduction of peroxides and repair of peroxides membrane, utilization of dietary lipids and

alternative biological pathways that occur in different type of cancer, multiple system organ failure and diabetes. Synthetic antioxidants are found to be harmful to the health, so as alternative natural antioxidants from plant source are safer to health and have better antioxidant activity. Considerable evidences suggest that plant biomolecules such as 6-gingerol ,Caffeic acid, Cyanidin ,Equol, Fisetin ,Myricetin ,Quercetin have anticancer property[10.11,12,24,25,30,37]. Plant flavonoids show efficacy against cardiovascular disease by inhibiting platelet aggregation and adhesion [68].Some phytochemicals have been shown to be hypolipidemic thus control the plasma cholesterol [21,19].On the other hand few plant biomolecules such as polyohenols (β-catechin, epicatechchin ,tannic acid, saponins etc.) demonstrated to have antidiabetic activity as they decrease or delay the transport of glucose to intestine by a variety of parthways [29,30,45,71]. phytochemicals like sulforaphane, resveratrol, curcumin and the cannabinoid THC show hormetic mechanism of action to prevent a number of neurodegenerative diseases[74-78]. Despite the importance of phytochemicals in prevention of diseases there are some challenges regarding its proper administration in the body because of their low water solubility, low absorptivity, low bioavailability and half life of oral phytochemicals are poor. To deal with such problem a strategy of engineered phytochemicals such as PEG-curcumin, nanocurcumin has developed. Engineered phytochemicals are with improved cellular permeability, proteolytic stability and enhanced half-life of cells. Thus by increasing effective size, solubility in aqueous medium and thereby increasing circulation half life; without disturbing rather enhancing bioactivity engineered phytochemicals are now of immense interest in the area of targeted phytochemical delivery. The latest trend of rethinking the natural sources for health and medicine has created a lot of development but still there is much to be learnt about their metabolism, bioavailability, mode of action and dose-response effect, physical, chemical properties such as solubility, diffusion and temperature effects of the phytochemicals of interest and in some cases the actual compound responsible for health effects are still unknown. So, further research is needed to ensure high yield as well as viability and bioavailibity of the plant biomolecules.

Acknowledgement: Authors are grateful to the Vice-Chancellor, University of Kalyani, Kalyani, Nadia, for his interest and support in this work.

References:

1. Schippmann U., D. Leaman & A. B. Cunningham. 2006. A comparison of cultivation and wild collection of medicinal and aromatic plants under sustainability aspects, en R. J. Bogers, L. E. Craker & D. Lange (eds.). *Medicinal and Aromatic Plants*, pp. 75-95. Springer, the Netherlands.
2. Massardo F. & R. Rozzi. 1996. Usos medicinales de la flora nativa chilena. *Ambiente & Desarrollo* **12**: 76-81.
3. He S. A. & Y. Gu. 1997. The challenge for the 21st Century for Chinese botanic gardens, en D. H. Touchell & K. W. Dixon (eds.). *Conservation into the 21st Century*, pp. 21-27. Kings Park and Botanic Garden, Perth
4. Shiva V. 1996. *Protecting our biological and intellectual heritage in the age of biopiracy*. The Research Foundation for Science, Technology and Natural Resources Policy, New Delhi.
5. Toledo V. M. 1995. New paradigms for a new ethnobotany: reflections on the case of Mexico, en R. E. Schultes & S. von Reis (eds.). *Ethnobotany: evolution of a discipline*, pp. **75-88**. Chapman and Hall, London
6. Moerman D. E. 1998. Native North American food and medicinal plants: epistemological considerations, en H. D.V. Prendergast, N. L. Etkin, D. R. Harris & P. J. Houghton (eds.). *Plants for food and medicine*, pp. 69-74. Proc. Joint Conference of the Society for Economic Botany and the International Society for Ethnopharmacology, Royal Botanic Gardens, Kew.
7. Addae-Mensah I. 2000. Plant biodiversity, herbal medicine, intellectual property rights and industrially developing countries, en H. Lauer (ed.). G*hana: Changing values/changing technologies*, pp. 165-182. Council for Research in Values and Philosophy, Washington, DC.
8. Engelman, J. A. & Cantley, L. C. Chemoprevention meets glucose control. *Cancer Prevention research. (Phila)* **3**, 1049–1052 (2010).
9. Sherr, C. J. & Roberts, J. M. CDK inhibitors: positive and negative regulators of G1-phase progression. *Genes Development.* **13**, 1501–1512 (1999).
10. Shim JH, Su ZY, Chae JI, Kim DJ, Zhu F, Ma WY. Epigallocatechin gallate suppresses lung cancer cell growth through Ras-GTPase-activating protein SH3 domain-binding protein 1. *Cancer Prevntion Research (Phila Pa)* 2010; 3:670–679.
11. Lee, K. M. *et al.* Kaempferol inhibits UVB-induced COX-2 expression by suppressing Src kinase activity. *Biochemical Pharmacology.* **80**, 2042–2049 (2010).
12. Cho YY, Bode AM, Mizuno H, et al. A novel role for mixed-lineage kinase-like mitogen-activated protein triple kinase α in neoplastic cell transformation and tumor development. *Cancer Research*.2004; **64**:3855–64.
13. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *American Journal of Clinical Nutrition* 2005; **81**(1 Suppl): 230S–242S.

14. Erlund I, Meririnne E, Alfthan G, Aro A. Plasma kinetics and urinary excretion of the flavanones naringenin and hesperetin in humans after ingestion of orange juice and grapefruit juice. *Journal of Nutrition* 2001; **131**(2):235–241. [PubMed: 11160539]
15. Lee, K. M. 5-deoxykaempferol plays a potential therapeutic role by targeting multiple signaling pathways in skin cancer. *Cancer Prevtion. Research. (Phila Pa)* **3**, 454–465 (2010).
16. Kuijsten A, Arts IC, Vree TB, Hollman PC. Pharmacokinetics of enterolignans in healthy men and women consuming a single dose of secoisolariciresinol diglucoside. *Journal of Nutrition* 2005;**135**(4):795–801.
17. Funk, C. D. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* **294**, 1871–1875 (2001).
18. Ermakova, S. P. (-)-Epigallocatechin gallate overcomes resistance to etoposide-induced cell death by targeting the molecular chaperone glucoseregulated protein 78. *Cancer Research.* **66**, 9260–9269 (2006).
19. Shim, J. H. *et al.* Epigallocatechin gallate suppresses lung cancer cell growth through Ras-GTPase-activating protein SH3 domain-binding protein 1. *Cancer Prevention Research (Phila Pa)* **3**, 670–679 (2010).
20. Palermo, C. M., Westlake, C. A. & Gasiewicz, T. A. Epigallocatechin gallate inhibits aryl hydrocarbon receptor gene transcription through an indirect mechanism involving binding to a 90 kDa heat shock protein. *Biochemistry* **44**, 5041–5052 (2005).
21. Dirsch VM, Gerbes AL, Vollmar AM. Ajoene, a compound of garlic, induces apoptosis in human promyeloleukemic cells, accompanied by generation of reactive oxygen species and activation of nuclear factor kappaB. *Molecular Pharmacology* 1998;**53**:402–7.
22. Li, M. Direct inhibition of insulin-like growth factor-I receptor kinase activity by (–)-epigallocatechin-3-gallate regulates cell transformation. *Cancer Epidemiology. Biomarkers Prevention.* **16**, 598–605 (2007).
23. Yang JY, Della-Fera MA, Nelson-Dooley C, Baile CA. Molecular mechanisms of apoptosis induced by ajoene in 3T3-L1 adipocytes. *Obesity Research* 2006;14:388–97.
24. Funk, C. D. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* **294**, 1871–1875 (2001).
25. Shephard SE, Zogg M, Burg G, Panizzon RG. Measurement of 5-methoxypsoralen and 8-methoxypsoralen in saliva of PUVA patients as a noninvasive, clinically relevant alternative to monitoring in blood. *Archives of Dermatological Research* 1999;**291**(9):491–499.

26. Byun, S. Luteolin inhibits protein kinase C(epsilon) and c-Src activities and UVB-induced skin cancer. *Cancer Research.* **70**, 2415–2423 (2010).
27. Samuelsson, B., Dahlen, S. E., Lindgren, J. A., Rouzer, C. A. & Serhan, C. N. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. *Science* **237**, 1171–1176 (1987).
28. Undevia SD, Gomez-Abuin G, Ratain MJ. Pharmacokinetic variability of anticancer agents. *Nature Reviews Cancer* 2005;**5(6)**:447–458.
29. Fisher, R. P. CDKs and cyclins in transition(s). *Current. Opinion on Genetic. Development.* **7**, 32–38 (1997).
30. Kang, N. J. Equol, a metabolite of the soybean isoflavone daidzein, inhibits neoplastic cell transformation by targeting the MEK/ERK/p90RSK/ activator protein-1 pathway. *Journal. Biological. Chemistry.* **282**, 32856–32866 (2007).
31. Lee, K. M. Kaempferol inhibits UVB-induced COX-2 expression by suppressing Src kinase activity. *Biochemical Pharmacology* **80**, 2042–2049 (2010).
32. Cho, Y. Y. *et al.* A regulatory mechanism for RSK2 NH(2)-terminal kinase activity. *Cancer Research* **69**, 4398–4406 (2009).
33. Yang JY, Della-Fera MA, Nelson-Dooley C, Baile CA. Molecular mechanisms of apoptosis induced by ajoene in 3T3-L1 adipocytes. *Obesity Research 2006*; **14:388**–97.
34. Lu, H., Chang, D. J., Baratte, B., Meijer, L. & Schulze-Gahmen, U. Crystal structure of a human cyclin-dependent kinase 6 complex with a flavonol inhibitor, fisetin. *Jornal of Medical Chemistry* **48**, 737–743 (2005).
35. Goldin BR. In situ bacterial metabolism and colon mutagens. *Annual Review of Microbiology* 1986;**40**:367–393.
36. Keppler K, Humpf HU. Metabolism of anthocyanins and their phenolic degradation products by the intestinal microflora. *Bioorganic Medical Chemistry* 2005;**13**(17):5195–5205
37. Dirsch VM, Gerbes AL, Vollmar AM. Ajoene, a compound of garlic, induces apoptosis in human promyeloleukemic cells, accompanied by generation of reactive oxygen species and activation of nuclear factor kappaB. *Molecular Pharmacology* 1998; **53**:402–7.
38. Rechner AR, Smith MA, Kuhnle G, Gibson GR, Debnam ES, Srai SK, et al. Colonic metabolism of dietary polyphenols: influence of structure on microbial fermentation products. *Free Radical Biology and Medicine* 2004; **36**(2):212–225.

39. Atkinson C, Frankenfeld CL, Lampe JW. Gut bacterial metabolism of the soy isoflavone daidzein: exploring the relevance to human health. *Experimental Biology and Medicine (Maywood)* 2005;**230**(3):155–170.
40. Kang, N. J. Delphinidin attenuates neoplastic transformation in JB6 Cl41 mouse epidermal cells by blocking Raf/mitogen-activated protein kinase kinase/ extracellular signal-regulated kinase signaling. *Cancer Prevntion Research (Phila Pa)* **1**, 522–531 (2008).
41. Oi, N. Resveratrol, a red wine polyphenol, suppresses pancreatic cancer by inhibiting leukotriene a4 hydrolase. *Cancer Research:* **70**, 9755–9764 (2010).
42. Undevia SD, Gomez-Abuin G, Ratain MJ. Pharmacokinetic variability of anticancer agents. *Nature Reviews Cancer* 2005; **5**(6):447–458.
43. Shoji Y and Nakashima H 2004 *J. Drug Targ.* 12 385
44. Commandeur JNM, Vermeulen NPE. (1996). Cytotoxicity and cytoprotective activities of natural compound. The case of curcumin. *Xenobiotica,* **26:** 667-668.
45. Jung, S. K. Myricetin suppresses UVB-induced wrinkle formation and MMP-9 expression by inhibiting Raf. *Biochemistry Pharmacology* **79**, 1455–1461 (2010).
46. Lee, K. M. 5-deoxykaempferol plays a potential therapeutic role by targeting multiple signaling pathways in skin cancer. *Cancer Prevention Research. (Phila Pa)* **3**, 454–465 (2010).
47. Jagetia ,G.C.,Baliga,S.M.,2002e.The evaluationof the radioprotectiveeffect of chyavanaprasha(an ayurvedic rasayana drug) in the mice exposed to lethal dose of γ-radiation:a preliminary study. *Phytotherapy research.*
48. Yonezawa M, Katoh N, Takeda A. 1989. Radiation protection by shigoka extract on split dose in mice. *Journal of Radiation Research* **30**: 247– 254
49. Miyanomae T, Frindel E. 1988. Radioprotection of haemopoiesis conferred by Acanthopanax senticosus Harms (Shigoka) administered before or after irradiation. *Experimental Hematology* **16**: 801–806.
50. Jagetia GC, Shirwaikar A, Rao SK, Bhilegaonkar PM. 2003d. Evaluation of the radioprotective effect of Ageratum conyzoides Linn. Extract in mice exposed to different doses of gamma radiation. *Journal of Pharmacy and Pharmacology* **55**: 51–58.
51. Bakina EE, Rodina Y, Kinzburskii, Kopytin BM. 1967. Use of P vitamins, quercetin and flavallicep during radiation sickness in rats. Vliyanie Organizm Fiz Khim Faktorov Vnesh Sredy Sb Rab Mater Nauch Konf 1967: 57–58.

52. Reeve VE, Bosnic M, Rosinova E, Boehm-Wilcox C. 1993. A garlic extract protects from ultraviolet B (280–320 nm) induced suppression of contact hypersensitivity. *Photochemical Photobiological science* **58**: 813–817.
53. Sato Y. 1990. Studies on chemical protectors against radiation. XXXI. Protection effects of Aloe arborescens on skin injury induced by x-irradiation. Yakugaku Zasshi **110**: 876– 884
54. Narimanov AA, Miakisheva SN, Kuznetsova SM. 1991. The radioprotective effect of extracts of Archangelica officinalis Hoffm. and Ledum palustre L. on mice. *Radiobiologiia* **31**: 391–393. Narimanov AA. 1993.
55. Liu CX, Xiao PG. 1993. Danggui (Angelica sinensis). An Introduction to Chinese Materia Medica. Beijing Medicinal University and Peking Union Medical University Press: Beijing, 168.
56. Ammon HP. 1993. Mechanism of antiinflammatory actions of curcumin and boswellic acids. *Journal of Ethnopharmacology* **38**: 113– 119.
57. Chaudhary D, Chandra D, Kale RK. 1999. Modulation of radioresponse of glyoxalase system by curcumin. *Journal of Ethnopharmacology* **64**: 1–7.
58. Agarwal SS, Singh VK. 1999. Immunomodulation: A review of studies on Indian medicinal plants and synthetic peptides. *Proc Indian National Academy of Science* **B65**: 79–204.
59. Belinky PA, Aviram M, Mahmood S, Vaya J. 1998. Structural aspects of the inhibitory effects of glabridin on LDL oxidation. *Free Radical Biology of Medicine* **24**: 1419–1429.
60. Kovalenko PG, Antonjuk VP, Maluita SS. 2003. Secondary metabolites production from transformed cells of Glycyrrhiza glabra and Potentilla alba producents of radioprotective compounds. *Ukraininca Biorganica Acta* **1**: 1–17.
61. Shetty TK, Satav JG, Nair CKK. 2002. Protection of DNA and microsomal membranes in vitro by Glycyrrhiza glabra L. against gamma radiation. *Phytotherapy Research* **16**: 576–578.
62. Smyshliaeva AV, Kudriashov Iu B. 1992. The modification of a radiation lesion in animals with an aqueous extract of Hypericum perforatum L. Nauchnye Doke Vyss Shkoly Biol Nauki **4**: 9–13.
63. Hsu HY, Yang JJ, Ho YJ, Lin CC. 1999. Difference in the effects of radioprotection between aerial and root parts of Lycium chinese. *Journal of Ethnopharmacology* **64**: 101–108.
64. Jagetia GC, Baliga MS. 2002a. Influence of the leaf extract of Mentha arvensis Linn. (mint) on the survival of mice exposed to different doses of gamma radiation. Strahlenther Onkol **178**: 91–98
65. Rao AV, Uma Devi P, Kamath R. 2001. In vivo radioprotective effect of Moringa oleifera leaves. *Indian Journal of Experimental Biology* **39**: 858–863.
66. sunila ES and Kuttan G,2005

67. Jagetia GC, Baliga MS, Malagi KJ, Kamath SM. 2002. The evaluation of radioprotective effect of triphala (an Ayurvedic rejuvenating drug) in the mice exposed to gamma-radiation. *Phytomedicine* **9**: 99–108.
68. Lee, K.W., Kang, N.J., Rogozin, E.A; *Myricetin* is a *novel natural inhibitor* of *neoplastic cell transformation* and. *MEK1*. *Carcinogenesis* ***28***:*1918-1927* (*2007*).
69. Jung, S. K. Myricetin suppresses UVB-induced skin cancer by targeting Fyn. *Cancer Research.* **68**, 6021–6029 (2008).
70. Molavi B and Mehta J L 2004 *Current Opinion on Cardiology* **19** 488.
71. Kim, J. E. MKK4 is a novel target for the inhibition of tumor necrosis factor-alpha-induced vascular endothelial growth factor expression by myricetin. *Biochemical Pharmacology* **77,** 412–421 (2009).
72. Kwon, J. Y. Delphinidin suppresses ultraviolet B-induced cyclooxygenases-2 expression through inhibition of MAPKK4 and PI-3 kinase. *Carcinogenesis* **30**, 1932–1940 (2009).
73. He, Z.Fyn is a novel target of (-)-epigallocatechin gallate in the inhibition of JB6 Cl41 cell transformation. *Moecularl Carcinogenesis* **47**, 172–183 (2008).
74. Commenges D, Scotet V, Renaud S,2000; Staehelin HB, Perrig-Chiello P, Mitrache C 2005.
75. Flight, I., & Clifton, P. (2006). Cereal grains and legumes in the prevention of coronary heart disease and stroke: a review of the literature. *European Journal of Clinical Nutrition,* **60** (10), 1145-1159.
76. Stromberg, I, Gemma, C, Vila, J, and Bickford, PC. 2005. "Blueberry and Spirulina-enriched diets enhance striatal dopamine recovery and induce a rapid, transient microglia activation after injury of the rat nigrostriatal dopamine system." *Journal of Experimental Neurology* **196**(2):298-307.
77. Joseph JA, Denisova NA, Arendash G, Gordon M, Diamond D, Shukitt-Hale B, Morgan D (2003) Blueberry supplementation enhances signaling and prevents behavioral deficits in an Alzheimer disease model. *Nutritional Neuroscience* **6:**153–162.
78. Wang, B., T. Li Y.H. Ding, R.H Zhang and H.J Wang, 2005: East Asian-Western North Pacific monsoon: A distinctive component of the Asian-Australian monsoon system. In: The Global Monsoon Systemt: Research and Forcast. Ed. by C.-P Chang, Bin Wang and N.-C.G Lau, WMO/TD No. 1266 (TMRP Report No. 70), 72-79.
79. Tchantchou, F., Apple juice concentrate prevents oxidative damage and impaired maze performance in aged mice. Journal of Alzheimer's Disease, 2005. **8**(3): p. 283
80. Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. American journal of clinical nutrition**...** *2006* Dec;84(6):1554.

81. Jeong, C. H. [6]-Gingerol suppresses colon cancer growth by targeting leukotriene A4 hydrolase. *Cancer Research.* **69**, 5584–5591 (2009).
82. Cho, Y. Y. A regulatory mechanism for RSK2 NH(2)-terminal kinase activity. *Cancer Research*. **69**, 4398–4406 (2009).
83. Davies, D. R. Discovery of leukotriene A4 hydrolase inhibitors using metabolomics biased fragment crystallography. *Journal of Medical Chemistry* **52**, 4694–4715 (2009).
84. Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A and Maitra A. Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): a novel strategy for human cancer therapy. *Journal of nanobiotechnology.* 53 (2007).