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Search for medicinal plants as a source of anti-inflammatory and anti-arthritic agents - A review

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ABSTRACT - Inflammatory diseases including different types of rheumatic diseases are a major and world wide problem. Gastrointestinal side effect is the major problem associated with the presently available non-steroidal anti-inflammatory agents. Now a days world population moves towards herbal remedies for treatment of such ailments. The number of plants have been screened for their anti-inflammatory and anti-arthritic activity, but only few of them reached up to the clinical level. This problem is mainly due to purely academic oriented research. Researchers have to lay emphasis on the phytoconstituents obtained form that plant for the specific treatment of such disease and not only to increase the number of plants having anti-inflammatory activity but have to work towards tapping their therapeutic utility.

KEY WORDS - Anti-inflammatory, anti-arthritic, Gastrointestinal track, herbal products.

INTRODUCTION

Inflammatory diseases including different types of rheumatic diseases are a major cause of morbidity of the working force throughout world. This has been called the 'King of Human Miseries' (1). Although rheumatism is one of the oldest known diseases of the mankind and affects a large percentage of population of the world, no substantial progress was seen till the synthesis of aspirin in 1899 by the German Company Bayer, the hint of which also was obtained from a plant, the Willow bark (*Salix alba*) used world wide in folk medicine for the relief of aches, fever and rheumatic pain. Since then many compounds were introduced as a result of laboratory search for drugs with anti-inflammatory activity (AIA); though many of them produced a dramatic symptomatic improvement in rheumatic processes, did not arrest the progress of the diseases process and all of them shared the common side effect i.e., gastro-intestinal irritations(2).

In India, many Ayurvedic practitioners are using various indigenous plants for the treatment of different types of arthritic conditions. Although the application of these medicaments has a sound tradition and a rational background according to the Indian system of medicine, perhaps it is essential to investigate the rationality of their use in modern scientific terms. The scientific studies to work out the actual efficacy and other limitations to these drugs would definitely widen their scope for future use if they come out to be really effective. This is particularly important, firstly due to the gravity of the problem of rheumatism and arthritis and secondly due to the absence of the right type of drug of synthetic origin for its treatment. The presently available drugs provide only symptomatic relief and are not free from side effects. The target should be to discover newer drugs from plant kingdom which may provide therapeutic cure and would be free from undesirable effects as well as economical, which would be accepted by the developing nations like India(3).

A systemic study of anti-inflammatory effects of Indian medicinal plants began by Gujral and his associates in 1956 and they screened a number of plants for their anti-arthritic effects. Subsequently, various workers from different laboratories in India have made significant contribution. Gujral and Saxena (1956), Karandikar et al. (1960), and others in the sixties mainly used formaldehyde induced arthritis (Brownlee,

1950) and Croton oil induced granuloma pouch in rats (Selya, 1958), as the experimental models of inflammation. Later, with the introduction of better and more specific models of experimental inflammation like carrageenan induced paw edema in rats (Winter et all 1950), Cotton pellet induced granuloma in rats (Winter et al 1958), Freud's complete adjuvant induced arthritis (Newbould, 1968) etc. workers in different laboratories tested their drugs with the help of the later models. Scientists in Central Drugs Research Institute, Lucknow have studied nearly two thousand Indian medicinal plants for their various pharmacological properties (1).

The greatest disadvantage in the presently available potent synthetic anti-inflammatory drugs lies in their toxicity and reappearance of symptoms after discontinuation. Therefore, the search for their AIA is an unending problem (4, 5).

Table No.1 - Active Principles that have been isolated from the Indian Medicinal Plants having anti-inflammatory activity (1)

Nature of the Compounds	Name of the Compounds	Plants	Animals Models used to detect anti-inflammatory Activity
Alkaloids	Total alkaloids	*Allangian lamarcki*	3 & 5
	Berberine	*Berberis aristata*	1, 2 & 3
	Tylophorine	*Tylophora Indica*	1,2&5
	Crotalaburnine	*Crotalbria-laburnifolia*	1,2,3 & 7
Flavonoids	Epicatechin	*Anacardium-Occidentala*	1,2,3&4
	Gossypin	*Hibiscus-vitifolius*	1,5&9
	Bavachinin	*Psarales coryfolia*	1,6&8
	Nepitrin	*Nepta Hindostana*	3,4&10
	Lanceolarin	*Dalbergia-lanceolaria*	1&3
	Taxifolin	*Madhuca-Longifolia*	1&3
Xanthone	Mangiferrin	*Causeora-decussata*	1,2&3
	Mesuazanthone-B, Euxanthone	*Mesua ferra*	1,2&5
	Mangostin	*Garcinia-Mangostana*	4
	Dehydrocylogua-nadine, callophllin-B	*Callophyllum innophyllum*	1,2&5
Others	Curcumin	*Curcuma longa*	1,2,3 & 4
	Nimbidin	*Azadirachta indica*	1,3&5
	β-sitosterol	*Cyperus rofundus*	1,2&8
	Callophyllolide	*Callophyllum innophyllum*	1,2,3 & 4
	Vitoxin	*Ochrocurpus-Longifolius*	1,2
	Dysobinin	*Dysoxylum-hinectariferum*	1
	Gangetin	*Desmodium-gangeticum*	1,2,6&8
	Nimbin	*Malia indica*	1,3
	Hedragenin	*Blighia sapids*	1,3
	Glycyrrhizin	*Glycyrrhiza-glabra*	3,4,8
	Glycyrrhetinic acid	*Glycyrrhiza-glabra*	2

Animal Models:

1) Carrageenan induced oedema
2) Cotton pellet induced granuloma
3) Formaldehyde induced arthritis
4) Freund's complete adjuvant induced arthritis
5) Granuloma pouch
6) Writhing response
7) Anti-hyulaluronidase acti

8) Pyrexia

9) Mediator-induced oedema

10) Turpentine induced pleurisy

Phenolic Compounds with AIA.

The petroleum ether extract of the rhizomes of *Curcuma longa* (turmeric) showed significant anti-inflammatory activity (AIA) and was effective in delayed hypersensitivity. In granuloma pouch method, the water extract was the most potent with activity comparable to Indomethacin (6, 7).

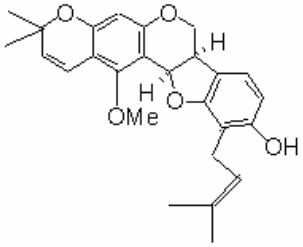
Curcumin, a constituent of turmeric, chemically, known as diferuloylmethane has been shown to be effective (8). It is as potent as Phenylbutazone in the carrageenan induced oedema test but half as potent in chronic tests. In subacute inflammation models in rats, it is found to be a stabilizer of lysosomal membrane (more potent than Ibuprofen) and as an uncoupler of oxidative phosphorylation (9). Two naturally occurring curcumin-related analogues, feruloyl-4-hydroxycinnamoylmethane and bis (4-hydroxycinnamoyl) methane, have shown AIA. Water soluble sodium curcuminate showed better AIA than curcumin in albino rats. The potencies of the curcumin analogues and Phenylbutazone in the carrageenan oedema, cotton pellet granuloma tests were in the order: sodium curcuminate > tetrahydrocurcumin > curcumin > phenylbutazone > triethylcurcumin (10).

Epicatechin, isolated from seed coat of *Anarcadium occidentale* appears to be atleast as effective as Phenylbutatazone against various test models (11). Bergenin, isolated from the pods of *Peltophorum pterocarpum* was found to be equipotent to phenylbutazone in rats against carrageenan induced oedema (12).

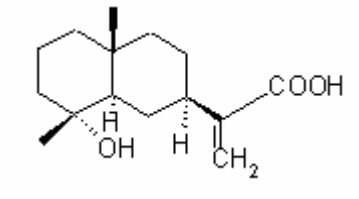
Flavanoids with AIA.

The flavanoid glycoside, chrysoeriol 7-0-β-D glucopyranosyl (2→1) -D-apiofuranoside isolated from *Dalbergia volubilis* exhibited AIA (13). A flavanoid from *Hedychium spicatum* showed a significant activity with less ulcerogenic index than Phenylbytazone (14). Two new flavano flavanone glycosides, diinsininol and diinsinin from rhizomes of *Sacropthyte piriei* (Balanophoraceae), showed IC_{50} values of Prostaglandin Synthesis Inhibition 9-20 µm and 13-14 µm respectively and in the inhibition of platelet-activating-factor-induced exocytosis, IC_{50} values of 49 and 39 µm, respectively (15). Three flavanoids, Phospholipase A_2 (PLA_2) inhibitors were isolated from a methanol extract of bark of the Samoan medicinal plant *Erythrina variegata* [Leguminosae] and identified as (i) 4'-hydroxy-3', 5'-diprenylisoflavanone (ii) 4'-hydroxy-6, 3', 5'-triprenylisoflavanone (iii) 3, 9-dihydroxy-2, 10-diprenylprterocarpene (erycrystagallin) (16).

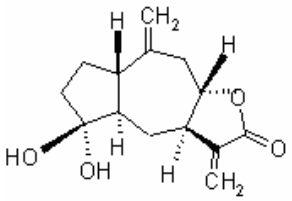
6, 3', 5'-triprenylisoflavanone



Ilicic Acid



Inuvisolide



The compound-Dicadalenol, Caryolane-1, 9 β-diol and quercetin were the most active substances tested and displayed dose dependent activities, isolated from aerial parts of *Heterotheca inuloide* (Asteraceae) (17). Quercetin, quercetin 3-0-rhamnoside (quercitrin) and quercetin 3-0-rutinoside (rutin) from 80% MeOH extract of leaves of *Morinda morindoides* (Rubiaceae) showed similar inhibition of classical pathway of complement system(18). The dichloromethane extract of the aerial parts of *Tanacetum microphyllum* (Compositae) yielded two anti-inflammatory flavanoids: 5, 7, 3'-trihydroxy-3, 6, 4'-trimethoxy flavone (Centaureidin) and 5, 3'-dihydroxy-4'-methoxy-7-carbomethoxyflavonl (19). Three flavanoids, isolated from *Inula viscosa* (Asteraceae) dichloromethane extract were 7-0-methylaromadendrin, rhamnocitrin, and 3-0-acetylpadmatin along with a sesquiterpene lactone inuvisolide; a sesquiterpene acid, ilicic acid; and a diagalactosyl-diacylglycerol, inugalactolipid A and shown to have 12-0-tetradecanoylphorbol-13-

acetate induced ear edema inhibitory activity in mice (20). Various flavanoid subtypes have shown to inhibit the COX-1/COX -2 catalyzed prostaglandin (PG) biosynthesis in vitro. These classes are discussed below (21, 22, 23).

Coumarins with AIA.

Calophylolide from the nuts of *Calophyllum inophyllum* (Clusiaceae) effectively reduced the increased permeability induced by the chemical mediators involved in inflammation, like histamine, serotonin and bradykinin. The ED_{50} was found to be 144.1, 250 and 135.5 mg/kg p. o., respectively against these mediators (24, 25). Four coumarins, 7-methoxycoumarin (herniarin), 6, 7-dihydroxycoumarin (aesculetin), 6-methoxy-7-glucosidylcoumarin (Scopolin), and 6-hydroxy-7-methoxycoumarin (Scopoletin), were isolated from the EtoAc extract of the flower tops of *Santolina oblongifolia* Boiss. (Compositae) The isolated compounds showed marked activity as inhibitors of Eicosanoid-release from ionophore stimulated mouse peritoneal macrophages (26).

Xanthones with AIA.

Magniferin, a xanthon C-glucoside from *Canscora decussatta*, mangostin and related compounds from *Garcinia mangostana* (27) and xanthones from *Calophyllum inophyllum* and *Mesua ferrea* are shown to have anti-inflammatory activity (28).

Terpenoids with AIA.

i. Triterpenoids.

The triterpenoids of the oleanene and ursene series were found to be active against carrageenan induced oedema and formaldehyde-induced oedema and formaldehyde-induced arthritis in rats. It has been suggested that the anti-inflammatory activity of the triterpenoids of the oleanene series with the polarity of compounds which is enhanced by the number of hydroxyl groups in the molecule (29).

Oleanolic acid 3-β-glucoside isolated from the seeds of *Randia dumetorum* (25-500 mg/kg, p.o.) showed a significant AIA in the exudative and proliferative phases of inflammation in rats (30). Salai guggal, the oleogum of *Boswellia serrata*, has been shown to process anti-inflammatory and anti-arthritic activities. It was shown to be effective in controlled clinical trials in arthritic patients. Its activity may be due to the boswellic acids present in the oleogum (31, 32, 33, 34). Two new triterpene saponins having phospholipase D inhibitory activity were isolated from methanol extract of the leaves of *Myrsine australis*. First is 3-0 {-β-D-xylopyranosyl-(1→2)-0-β-D-glucopyranosyl-(1→4) { 0-β-D-glucopyrnosyl-(1→2) }-α-L-arabinosyl} 16 α-hydroxy-13 β, 28-epoxyoleanane and second is 3 β-0-{-β-D-rhamnopyranosyl-(1→2)-0-β-D-glucopyranosyl-(1→4)-{0-β-D-glucopyrnosyl}-α-L-arabinopyranosyl}-16-α-hydroxy-13 β, 28-epoxyoleanane. Both compounds showed IC_{50} values of 3 and 2 µm, respectively, versus phorbol 42-myristate 13-acetate stimulated phospholipase D in human promylocytic lukemic (Hl-60) cells. Both compounds also inhibited FMLP (formyl-Met-Leu-Phe) stimulated Phospholipase D with IC_{50} values of 8 and 24 µm, respectively (35).

Two oleane type triterpene saponin, Zanhasaponins A and B and the cyclitol pinitol isolated from the methanol extract of root bark of *Zanha Africana* (Sapindaceae) were active as inhibitors of phospholipase A2 (36). Pentacyclic triterpenes from the 11-keto-boswellic acid series were identified as the active principle ingredients of Boswellia resin, inhibiting the key enzyme leukotrine biosynthesis, 5-lipooxygenase, of the genuine boswellic acids characterized, 3-0-acetyl-11-keto-β-boswellic acid, AKBA proved to be the most potent inhibitor of 5-LOX (37).

ii. Diterpenoid.

A new diterpenoid, tolypodial has been established from the terrestrial cyanobacteria *Tolypothrix nodosa* (HT-58-2) Tolypodiol and its monoacetate derivative show potent AIA in mouse ear oedema assay (38).

iii. Sesquiterpene.

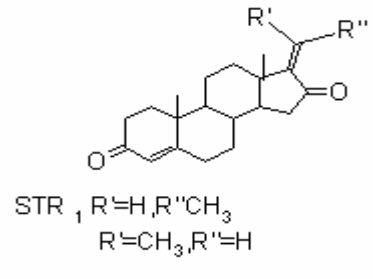
The antipyretic and AIA of a new sesquiterpene, spartidienedione isolated from *Psila spartioides* (Asteraceae) were evaluated in rabbits and guinea pigs. At a dose of 25 mg/kg, this substance showed AIA and antipyretic activity (39). Two new sesquiterpene cyclopentenones, dysidenones A, B and a new sesquiterpene aminoquinone, dysidine, all containing the same rearranged drimane skeletone have been isolated along with bolinaquinone from Sponge *Dysidea species*. Bolinaquinone, dysidine and a 1:1 mixture of dysidenones A and B significantly inhibited human Synovial Phospholiphase A_2 (PLA_2) at µm concentration. Compound shown an IC_{50} value of 2.0 µm and exert a higher potency and selectivity toward this enzyme than the reference inhibitor manoalide (40).

Steriods with AIA.

The oleoresin fraction of *Commiphora mukul* possesses significant anti-arthritic and anti-inflammatory activities. A steroidal compound isolated from *C.*

mukul displayed a significant activity which is dose dependent and more potent than the resin fraction present in *C. mukul*. A comparison of the anti-inflammatory activity of petroleum ether extra extractive of *C. mukul* with standard drugs showed the former to be effective as well. Guggal and yograjguggal were studied for their immunosuppresent activity in rabbits by using the Widal Agglutination test and the latter exhibited marked anti-inflammatory activity than the former.

The ethyl acetate-soluble potion of the resin (Guggulipid) on fractionation revealed that the acids display a significant anti-inflammatory activity while the neutral portion carries partially all hypocholesterolemic activity, while the neutral portion carries partially all hypocholesterolemic activity. It was soon found that neutral fraction contained several ketones, which exhibited a high lipid lowering activity. Further work led to the isolation of these compounds it was found that two steroids, named Z-and E-guggalsterone are responsible for the activity of the resin. The former has shown in rats to have a thyroid-stimulating action, suggesting that this property may be contributing to anti-hyperlipidaemic activity of the oleoresin (41, 42).



Here 1=Z-guggalsterone and 2=E-guggalsterone

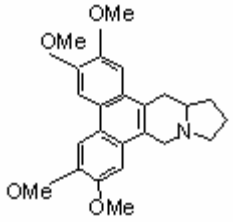
β-sitosterol isolated from *Cyperus rotendus* possessed potent anti-inflammatory activity against carrageenan and cotton pellet-induced oedema in rats and was comparable to Hydrocortisone and Oxyphenbutazone (43). The compound also possesses significant anti-pyretic activity (44). α-spinasterol obtained from the stem-bark of *Symplocos spicata* showed a significant activity against acute inflammation induced by carrageenan in rats and was more potent than Phenylbutazone but less potent than Betamethasone (45).

Polysaccharides with AIA.

The polysaccharide produced by *Serratia piscatorum* exhibited anti-inflammatory activity, which was completely lost when the polysaccharide was hydrolysed by acid or alkali into smaller molecules or when the hydroxyl groups were partially acetylated. The presence of hydroxyl groups in the macromolecules polysaccharide moiety may be playing an important role in the manifestation of anti-inflammatory activity (46).

Alkaloids with AIA.

Tylophorine from *Tylophora indica*, apart from the anaphylactic and immunocytoadherence action, significantly inhibited the primary and secondary responses of adjuvant-induced arthritis in rats (47, 48).



Tylophorine

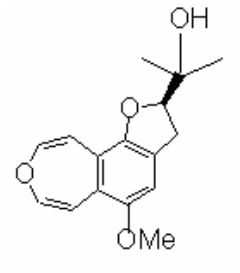
Four new bioactive Pyridinium alkaloids, named Spongidines A, B, C, D from sponge of the genus *Spengia* together with known Petrosaspongiolides D and G. All compounds significantly inhibited human Synovial Phospholipse A_2. (PLA_2) (49).

Miscellaneous agent with AIA.

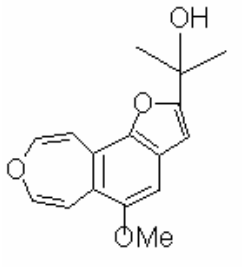
A glucosidic substance from leaves of *Dalbergia volubilis* (Papilionaceae) showed anti-inflammatory and anti-arthritis activities (50). Alcoholic extract of *Cardiosperum helicacabum* (Sapindaceae) leaves-showed significant anti-inflammatory activity in rats. *Cedrus deodara*, stem bark showed significant AIA in rat (51).

Gangetin, one of the pterocarpens, isolated from hexane extract of root of *Desmodium gangeticum* also produced a significant AIA in the exudative and proliferative phases of inflammation at 50 and 100mg/kg p. o. in rats (52). Researchers have found that n-tritriacontane at 100 mg/kg p. o. exhibits 51% AIA. A preliminary study revealed the presence of certain amino acids to suppress carrageen induced inflammation in rats, with cretinine the most active (53). Radiological findings evidently supported the long term anti-arthritis property of *Withania Somnifera* (Solanaceae) (54). Two new prenyl 3-benzoxepin derivatives, Perilloxn and Dehydroperillixin, were isolated from the dichloromethane extract of the stems of *Perilla frutescens* var *acuta,* their structures were elucidated as (-)-(R)-5-methoxy-2, 3-dihydrofuro (2, 3-g) benzoxepine and 5-methoxyfuro (2, 3-g)

benzoxepines, respectively. Both compounds possess inhibitory activities, with IC_{50} valves of 23.2 µm and 30.4 µm, respectively using an in vitro Cyclooxygenase-1 test (55).



Dihydrofurobenxepine



Methoxyfurobenxepine

3, 5-Di-0-Caffeoylquinic and 4, 5-di-0-caffeeoylquinic acids exhibited an appreciable anti-inflammatory activity in vitro isolated from leaf decoction of *Tessaria integrifolia* and *Mikania cordifolia.* (Asteraveae) (56). Details of clinical trial of *Zingiber officinale* is available and found useful. Delayed hypersensitivity in mice by the sheep RBC as an antigen was potentiated by the extract (57). Water soluble fraction of ethanol extract of leaves of *Nyctanthes arbertritis* orally administered to arthritic mice caused consistent depletion of TNF-α from the host plasma (58). Alcoholic fraction of *Cardiospermum halicabum* (250 mg/kg b. w., for 15 days) was tested on animals suffering from acute inflammation (hind paw oedema), drug significantly suppressed swelling of paw and weight of animals restored normal, acid phosphate in serum reduced which suggests anti-inflammatory action (59).

Suspension of dried powered leaves of *Vitex negundo* Linn (Verbenance) showed dose related inhibition of primary and secondary lesions induced by adjuvant (60). Study showed that Tripchloride from *Tripterygium wilfordii* is useful in the treatment of RA due to its inhibition of production of PGE_2 by synovial cells (61). There are various complex herbal preparations which are used as anti-arthritic agent (Table 2).

Table 2: Complex herbal preparations with anti-arthritic property.

Name of the preparation / plant	Reference Number
Ease	62
JCB	63
Tart Cherries	64
Oak Gass Extract	65
Pluembago zeylanica	66
Prosopis spicigera	67
Cactus grandiflorus	68
Indigofera asphalthoides	69
Wrightia tinctoria	70
Bougainvilliea spectabilis	71
Phyllanthus fraternus	72
nut-meg extract	73
Tinospora cardifolia	74

CONCLUSION

It is interesting to note that although a large number of plants have been studied and these investigations suggest selective anti-inflammatory activity of the said plants, at least in experimental models of inflammation, a large number of these studies have not been pursued further up to the stage of clinical trials. This may be due do the fact that most of the research work done in this field are purely academically oriented and there are no industrial supports behind these projects. However, only in few cases, the investigations were extended further and some active principles were isolated from crude plant extracts. Another shortcoming of these investigations is that, most of the studies did not report the effect of the plant extract or the purified fractions, on the gastrointestinal side effects, which are common undesirable effects associated with almost all non-steroidal anti-inflammatory drugs. There are however some drugs like *Boswellia serratta, Mesua ferra, Allium sativum,* etc. reports about this particular aspect of drug toxicity.

The above referred studies also did not report the toxic effects on liver and/or kidney and also detailed toxicity studies were not performed. Lastly most of the studies, even the recent ones did not report the effect of the test drugs (both purified and crude) on prostaglandin biosynthesis, since all the non-steroidal anti-inflammatory drugs inhibit prostaglandin biosynthesis, which is supposed to be the principal mode of action of these drugs.

Much money, time and energy have been spent in this field of research. So the reviewers believe that to get fruit of this labour, it is better not to increase the list but to reevaluate and test the anti-inflammatory effect of already reported plants to overcome the shortcomings pointed out earlier by approaching towards their phytoconstituents, to get better drugs for the relief of miseries of the suffering humanity and it is believed a superior therapeutically effective anti-inflammatory drug can be obtained from this source.

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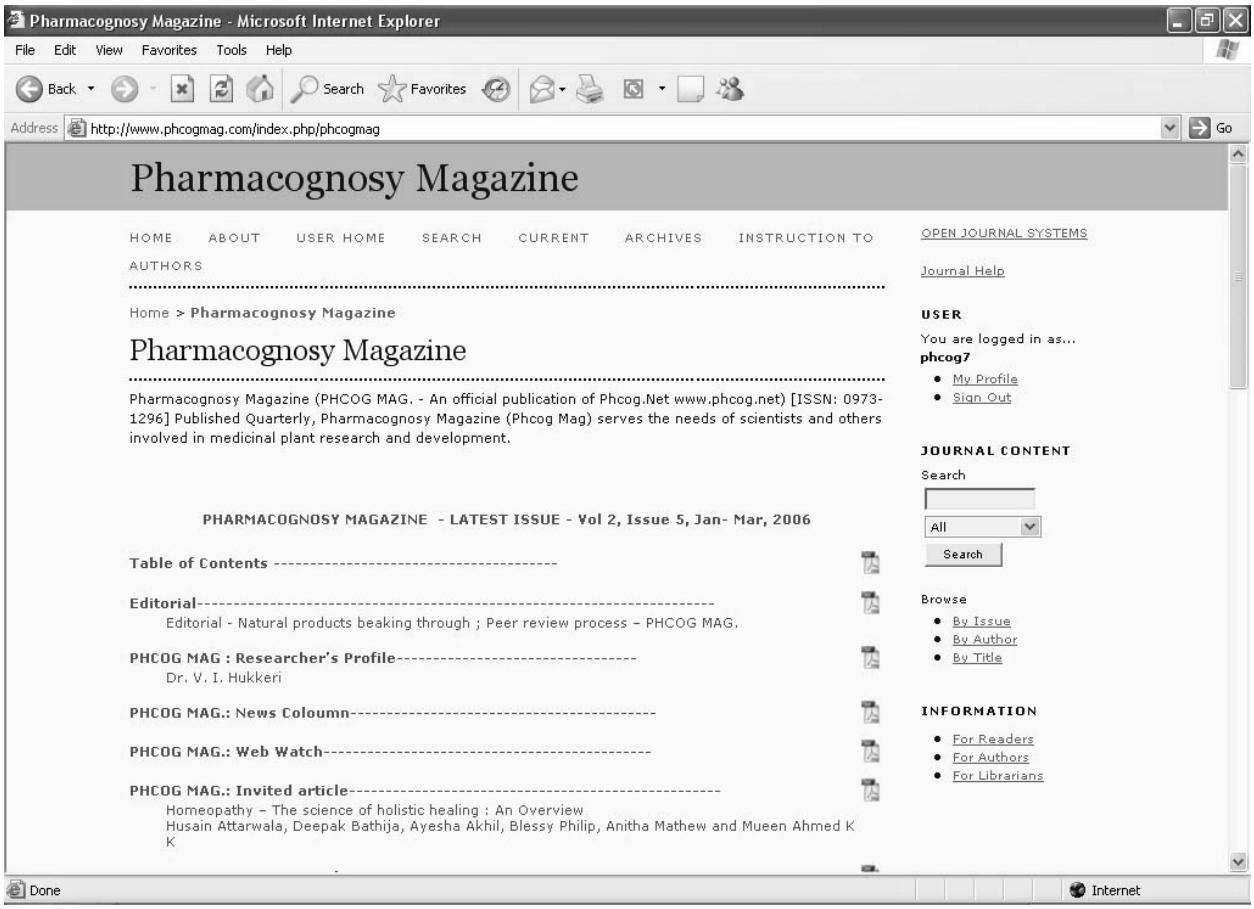

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