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Review

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Medicinal plants as a source of therapeutic agents against HIV infection

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Abstract

Many plants have been tested for anti-HIV activity. The present review covers the plants reported to be active against HIV.

Key words : HIV, AIDS, medicinal plants.

1. Introduction

The human immunodeficiency viruses (HIV) designated as HIV-1 and HIV-2 are the infection agents in human, causing a syndrome known as acquired-immuo deficiency syndrome at the terminal stage of the disease. HIV is a retrovirus (RNA virus) and belongs to the Lentivirus family (Lentus = slow) [1].

AIDS has grown more rapidly than the scientific advancement of understanding how to control the main causative agents. The global HIV epidemic is far more worse than previously thought, with about 1 in every 100 adults aged between 15-49 years being infected. According to UNICEF, presently over 30 million people are infected with HIV worldwide and about 16,000 new cases are added everyday.

The HIV virus consists of an outer lipid bilayer coat studded with surface glycoprotein (SUgp 120) and transmembrane glycoprotein (TMgp 41) complexes. Just beneath the lipid bilayer are matrix proteins (MA) and beneath that the virion consisting of internal capsule (CA) and nuclear capsid (NC) proteins which surround the single stranded RNA genome.

The centre region produces matrix, internal capsule and nuclear capsid proteins. The pole region produces enzymes like reverse transcriptase, integrase and protease [2]. Life cycle of HIV uses the mechanism of a host cell to replicate. HIV first attaches, then enters the host cell.

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Inside the host cell it uses reverse transcriptase to catalyze the formation of the viral DNA from the viral RNA genome. This viral DNA can then be integrated into the host cell's DNA where it is called proviral DNA. Once assimilated into the host genome, the proviral DNA can either actively produce the entire virus or it can remain latent and be replicated as the host cell divides [2, 3, 4].

2. Pathophysiological basis of HIV infection

HIV has a special affinity for CD4 + receptor bearing T lymphocytes (T helper cells). Nevertheless, other secondary or alternative receptor(s) may be needed for viral penetration, e.g. CD26, cell surface proteinase and galactosylcerebroside [5, 6]. The HIV infected cell turns into virus producing cell which will eventually be destroyed. Viral replication increases when the infected helper T cell is activated.

Newly produced viruses are liberated by 'budding' out from the host cell and they inturn infect more helper cells, eventually leading to their destruction. The presence of HIV in some helper cells may also provoke an autoimmune response against non-infected helper cells, causing further destruction of these important cells [7]. HIV infection also induces a premature programmed cell death (apoptosis) in infected helper T cells, which further depletes and diminishes i number [8].

Depletion of helper T cells leads to inefficient functioning of B lymphocytes as they require the 'help' of helper cells to produce specific antibodies. Cytotoxic CD8+T lymphocyte (Killer cells) activities are also impaired [9], causing a decreased ability of the immune system to destroy neoplastic and virus infected cells. Macrophages, having CD4+cell surface makers are also infected and destroyed [10], leading to diminished phagocytic response and a decreased ability of the body to defend itself against extracellular pathogens such as bacteria.

3. Enzymes in HIV chemotherapy

3.1 HIV-1 Protease

HIV protease is a C_2 symmetric homodimer in which each of the identical 99 amino acids subunit contribute a single aspartyl residue to the catalytic site. It is uniquely responsible for the post translational cleavage of the viral gag and gagpol polyproteins. Premature proteolysis in the cytoplasm would remove the N-terminal myristoyl glycine residue from the gag and gagpol polyproteins and presumably impair the ability of the viral proteins to aggregate at the cell membrane.

In the absence of competent protease, the reverse transcriptase has either low activity or is enzymatically inert. When the HIV protease is catalytically defective, viral maturation in HIV-infected cell culture is blocked and consequently infection is arrested [11-15].

3.2 HIV-1 Reverse Transcriptase (HIV RT)

It exists as a heterodimer consisting of lightly associated p51 and p66 subunits. The enzyme exert three distinct catalytic functions : (1) An RNA-dependent DNA polymerase activity (2) Utilizing the viral RNA strand as template, it synthesizes a complimentary strand of DNA (3) A DNA-dependent DNA polymerase to complete the synthesis of the double stranded proviral DNA. Therefore RT is responsible for the synthesis of double stranded viral DNA from proviral RNA for subsequent incorporation into the host cell chromosome [16].

3.3 HIV Integrase

It mediates a crucial step in the life cycle of HIV. The enzyme cleaves DNA ends in a sequence dependent manner and couples the

newly generated-04 groups to phosphates in the largest DNA. Three domains have been identified in HIV integrase (1) an - NH_2 terminal domain (2) a central catalytic core (3) A carboxy terminal DNA binding domain. Recently the - NH_2 terminal domain has been shown to consist of 3-alpha helices and a helical turn. The alpha helices form a 3-helix bundle that is stabilised by Zn-binding [17].

4. HIV Transmission : Modes and Routes

Transmission of HIV usually requires transfer of body fluids such as blood, semen, vaginal secretions that contain the virus or transfer of cells, especially macrophages containing viruses. HIV transmitted through (1) Sexual contact [18] (2) Exposure to infected blood components (3) Breast milk (4) Organ transplants (5) Artificial insemination with donated sperm (6) Vertical transmission (HIV positive mother to child) [19]. HIV is not transmitted by casual social contact such as sharing household facilities, glasses etc.

5. Plants reported to be active against HIV

There is an extensive area of forest enriched with plant diversity in the world. Several of these plants have been used as folklore medicines. However, the medicinal plant have rarely been investigated for anti-HIV activity. In HIV chemotherapy the inhibitory effect of plant extracts on HIV replication is usually monitored in terms of inhibition of virus-induced cytopathic effect in MT-4 cells. The MT-4 cells are infected with HIV and incubated at 37°C in a CO_2 incubator in the presence of the plant extracts. After five days, cell viability is measured by tetrazolium based colorimetric assay [20].

Inhibitors of HIV reverse transcriptase (RT) are important leads for the treatment of AIDS. Many natural products have been shown to be active as RT inhibitors. These compounds belongs to a wide range of different structural classes e.g. coumarins, tannins, flavonoids, alkoloids, terpenes, lignans, anthraquinones and polysacharides. Calanolide A, isolated from the terrestrial plant *Calophyllum lanigerum* (Guttiferae), has been discovered as the most interesting natural RT inhibitor [21].

Many compounds of plant origin have been identified that inhibit different stages in the replication cycle of HIV :

(1) Virus cell fusion: lectins (mannose and N-acetylglucosamine specific) and triterpenes (betulinic acid and their analogues); (2) Virus adsorption: phenolics (caffeic acid derivatives, catechinic acid derivatives, galloyl acid derivatives), isoquinoline alkaloids (michellamines), Chromone alkaloids (Schumannificine), tannins and triterpenes (Soyasaponin, glycyrrhizin and analogues); (3) integration : lignans (arctigenin and analogues), phenolics (curcumin), coumarine (3-substituted-4-hydroxycoumarins); (4) protease inhibition (proteolytic cleavage) : Xanthones (mangostin), saponins (ursolic and maslinic acid); (5) glycosylation : alkaloids such as piperidines (1-deoxynojirimicin), indolizidines (castanospermic), pyrrolizidines (anstraline); (6) translation : single chain ribosome inactivating proteins; (7) reverse transcription : alkaloids (benzophenanthridines, isoquinolines, quinolines, protoberberins), lactones (protolichesterinic acid), tannins and triterpenes [22].

A preliminary literature search has been conducted on investigation of medicinal plants mainly in Japan, Brazil, South Korea and Germany, in order to identify and study the chemical constituents of the plants, which could be responsible for their activity against this pathology. Potentialy active plants against HIV infection are listed in Table-1.

Table 1
Medicinal plants active against HIV

Plant	Occurrence	Used parts	Nature of extracts/compounds tested	Ref.
Acacia nilotica	Sudane	Bark, pods	MeOH extract	[23]
Acanthopanax koreanum	Korea	Stem bark	MeOH ext.	[24]
Acer okamotoanum	Korea	Leaves	Bioassay directed chromatographic fraction of ethyl acetate ext.	[25]
Achrocline flaccida	Argentina	Whole plant	Infusion	[26,27]
Acsculus chinensis Bge. (Hippocastanaceae)	North Western China	Seeds	EtOH extract	[28]
Agastache rugosa	Korea	Roots	MeOH ext.	[29,30]
Allanblackia stuhlmanii (Guttiferae)	Missouri	Leaves	Organic ext.	[31]
Aloe barbadensis Miller	India, Germany	Whole plant	-	[32]
Alternanthera brasiliana (Arnaranthaceae)	Brazil	Whole plant	Aqueous ext.	[33]
Ancistrocladus korupensis	USA, Korea, China	Leaves, Root	-	[34,35]
Andrographis paniculata (Acanthaceae)	India	Leaves, Shoots	Phase 1 dose escalating clinical trial of andrographolide	[36]
Annona squamosa L. (Annonaceae)	China	Fruits	MeOH ext. of fresh fruit	[37]
Anogeissus acuminata	USA	Stems	-	[38]
Anvillea gracinii	Saudi Arabia	aerial parts	-	[39]
Ardisia japonica (Tunb.) Bl. (Myrsinceae)	China	Roots	Decoction	[40]
Artemisia verlotorum (Asteraceae)	Italy	Leaves	Dried aqueous ext.	[41,42]
Astraglaus membranaceus	China	Whole plant	-	[43]
Berchemia berchemiaefolia	Korea	Bark	MeOH ext.	[28,44]
Boerhaavia caribea	-	Whole plant	-	[45]
Calophyllum lonigerum var. austrocoriaccum	Germany	Latex	-	[46,47]
Calophyllum cerasiferum (Clusiaceae)	Canada	Seeds	Hexane ext.	[48]
Calophyllum inophyllum (Clusiaceae)	Canada	Seeds	Hexane ext.	[48]
Calophyllum teysmanii var. inophylloide	USA	Latex	-	[46, 49]
Calophyllum cordatoblongum	Srilanka	Whole plant	-	[50]
Ceropegia juncea	India	Whole plant	-	[51]
Chamacyce hyssopifolia	Japan	Whole plant	water ext.	[52]
Chrysanthemum morifolium	USA	whole plant	-	[53]
Combretum glutinosum	-	Leaves	Isolated tannins	[54]
Conospermum incurvum	Australia	Whole plant	-	[55]

Cordia spinescens	Japan	Leaves	Water extract	[52]
Cordyceps sinensis	China	Whole plant	-	[43]
Crataegus pinnatifida	Korea	Leaves	MeOH ext.	[56]
Croton tiglium	Japan	Seeds	MeOH ext.	[57]
Cupressurs sempervirens	France	Whole plant	Proanthcyanidin polymer freaction	[58]
Curcuma domestica	Indian	Rhizome	-	[59]
Cydonia vulgaris (Rosaceae)	Italy	Aerial parts	$CHCl_3$-MeOH ext.	[60]
Eleutherine americana (Iridaceae)	Japan	Bulf	-	[61]
Enantia chlorantha	Cameroon	Whole plant	-	[62]
Equisetum arvensis	Korea	Aerial parts	Water ext.	[63]
Erythroxylum critifolium	USA	Whole plant	MeOH ext.	[64]
Erythroxylum lucidum	USA	Leaves	MeOH ext.	[64]
Eupatorium buniifolium	Argentina	Whole plant	Water ext. Organic ext.	[26,27]
Euphorbia kansui	Japan	Whole plant	-	[65]
Franocoeuria crispa	USA	Whole plant	Essential oil	[66]
Ficus carica	Korea	Leaves	Water ext.	[63]
Gamochaeta simplicanlis	Argentina	Whole plant	Lipophillic and Hydrophillic ext.	[26,27]
Geigeria alata	USA	Whole plant	Essential oil	[66]
Geum japonium Thumb (Rosaceae)	China	Whole plant	MeOH ext.	[67]
Gledilisia japonica	China	Fruit	Isolated triterpinoiol saponins	[68]
Glycyrrhiza uralensis	China	Whole plant	Water ext.	[43]
Gymnocladus chinensis	China	Fruits	Isolated triterpinoid saponins	[68]
Glycyrrhiza uralensis	China	Whole plant	Water ext.	[43]
Gymnocladus chinensis	China	Fruits	Isolated Triterpinoid saponins	[68]
Hamelia axillaris	Panama	Leaves	MeOH ext.	[64]
Helichrysum bracteatum	India	Flowers	Isolated phenolic component	[69]
Hibiscus syriacus	Korea	Leaves, stem	MeOH ext.	[63]
Homalanthus nutans	USA	Whole plant	-	[70]
Houttuynia cordata	Korea	Whole plant	Steam distillate	[63,71]
Hypericum capitatum	Turkey	-	Crude ext. from cell culture	[72]
Hyptis capitata	Japan	Whole plant	Isolated triterpinoids	[73]
Hyptis lantanifolia	Japan	Aerial parts	Water ext.	[52]
Indigofera tinctoria	India	Whole plant	MeOH ext.	[74]
Ixeris tamagawaensis	Korea	Aerial parts	Water ext.	[63]
Jatropha curcas Zaire	Japan	Leaves, branches	Water and MeOH ext.	[52, 75]

Plant	Occurrence	Used parts	Nature of extracts/compounds tested	Ref.
Kadsura interior	China	Whole plant	-	[76]
Kadsura lancilimba How. (Schizandraceae)	Southern China	Stem, Roots	Diethyl ether ext.	[77]
Leitneria floridana Chapman (Leitneriaceae)	Southern Atlantic & Gulf Coastal Plain of US	Whole plant	Diethyl ether ext.	[78]
Leonia cymosa	USA	Whole plant	-	[79]
Lindackeria Laurina	Panama	Leaves	MeOH ext.	[64]
Lindera erythrocarpa	Korea	Leaves	MeOH ext.	[44]
Lithospermum erythrorhizon	Japan	Root	Water ext.	[80]
Maclura tinctoria L. (moraceae)	New York	Bark	Organic ext.	[81]
Maprounca africana	Africa	Root	Isolated triterpenoid	[82,83]
Margyricarpus setosus	Italy	Aerial parts	Activity directed fractionation of ext.	[84]
Maytenus senegalensis	Japan	Stem bark	MeOH and water ext.	[85]
Merremia peltata (Convolvulaceae)	Japan	Whole plant	MeOH ext.	[86]
Ocimum sanctum	India	Leaves	Organic ext.	[87]
Panax japonicum	Japan	Rhizomes	Isolated triterpenoid	[88]
Panax zingiberensis	Japan	Rhizomes	Isolated triterpenoid	[88]
Phoradendrom juniperinum	Japan	Whole plant	Isolated triterpenoid	[73]
Phyllanthus sellowianus	Argentina	Whole plant	Infusion	[26]
Plantago asiatica	Japan	Whole plant	Isolated flavonoids	[89]
Prosopis glandulosa	Japan	Leaves & Twigs	Isolated Triterpenoids	[73]
Prunella vulgaris	Japan	Spikes	Water ext., Prunellin	[80, 105, 106]
Quercus pedunculata	Korea egypt	Fruit	Water ext.	[90]
Rodiola rosea	Korea	Root	MeOH ext.	[24]
Rosa wodsii	Japan	Leaves	Isolated Triterpenoids	[73]
Rosamarinus officinalis (Rosemary)	Slovenia	Whole plant	-	[91]
Rumex cytrius	Egupt	Fruit	Isolated Triterpenoids	[90]
Sambucus nigra L.	Spain	Bark	-	[92]
Schisandra sphacrandra stapf (Schisandraceae)	China	Stem	Isolated triterpenoid	[93]
Serijania mexicana	Panama	Whole plant	MeOH ext.	[64]
Siegesbeckia pubescens	Korea	Whole plant	MeOH ext.	[44]
Siutellaria baicalensis	China	Whole plant	-	[43]
Spathodea campanulata	Belgium	Stem bark	Polar fraction of decoction	[94]
Strychnos nux-vomica	India	Seeds	Organic ext.	[87]
Syringa dilatata	Korea	Leaves	Water ext.	[63]
Syzygium claviflorum	USA	Leaves	-	[73,95]

Tecomella undulata	India	Leaves	Petroleum ether - ethyl acetate fraction	[96]
Terminalia bellerica	India, Denmark	Fruit	-	[97]
Terminalia chebula	Egypt	Fruit	-	[90]
Terminalia horrida	Egypt	Fruit	-	[90]
Ternstromia gymnanthera	USA	Aerial parts	Isolated Triterpenoids	[73]
Tetrapeteris macrocarpa	Japan	Aerial parts	MeOH etc.	[52]
Toddalia asiatica	USA	Whole plant	Bioassay directed fraction	[98,99]
Tripterygium hypoglaucum	China	Root bark	MeOH ext.	[100]
Tripterygium wilfordii (Celastraceae)	China	Roots	MeOH ext.	[100]
Vismia cayenensis Pers. (Guttiferae)	Ecuador	Leaves	Organic ext.	[101]
Waltheria indica	Panama	Branches	MeOH ext.	[64]
Werneria ciliolata	Italy	Aerial parts	$CHCl_3$ ext.	[102]
Werneria dactylophylla	Italy	Aerial parts	$CHCl_3$ ext.	[102]
Xanthoceras sorbifolia Buxge (Sapindaceae)	Central Mangolia	Wood	MeOH ext.	[103]
Xylopia fructescens	Panama	Leaves bark	MeOH ext.	[64]

6. Conclusion

The continuing spread of infection with the human immunodeficiency virus and the limitations of currently available therapy have made the need for new drugs for the treatment of AIDS increasingly urgent. Recent advances in the understanding of HIV biochemistry have led to the identification of a number of biochemical targets in HIV against which selective agents could be developed [104].

There is an urgent need for investigation of the potential contribution of natural products to the development of new agents possessing activity against HIV on the basis of their mechanism of action. Further work on the extracts reported to be active against HIV may lead to active compounds useful in dealing with HIV infection.

References

1. Burger EA. (1998) *Nature* 391:240.

2. Hirsh M, D'Aquila RT. (1993) *New England Journal of Medicine* 328:1686.

3. Flier JS, Underhill LH, Crumpackers CS. (1985) *New England Journal of Medicine* 321:163.

4. Joshi UJ, Indu TB, Patil P. (2000) *Indian Drugs* 4:160.

5. Paramjit S, Sihorkar V, Jaitely V, Kanayjia P, Mishra V, Vyas SP. (2000) *Indian Drugs* 6:259.

6. Dalgleish AG. (1993) *Current AIDS Literature* 12:423.

7. Pantaleo G, Graziosi C, Fauci AS. (1993) *New England Journal of Medicine* 5:327.

8. Carson DA, Ribeiro JM. (1993) *The Lancet* 341:1251.

9. Buseyne F, Riviere Y. (1993) *AIDS* 7:581-585.

10. Fauci AS, Rosenberg ZF. (1994) In : Broder S, Merigan TC, Bolognesi D. (Eds.) *Textbook of AIDS Medicine*, Williams and Wilkins ; Baltimore : 55-76.

11. Pearl LH, Taylor WR. (1987) *Nature* 329:351.

12. Pearl LH, Taylor WR. (1987) *Nature* 328:482.

13. Ratner L, Haseltine W. (1985) *Nature* 313 : 277.

14. Peng, C, Ho BK, Chang TW. (1989) *J. Virol.* 63 : 2550.

15. Norbeck DW. (1990) *Annual Reports in Medicinal Chemistry* 25:149.

16. Kageyama S, Kurokawa M, Shiraki K. (2000) *Antivir Chem Chemother* 2:157-164.

17. Astrid PAM, Fusinita MI, Arnold V. (1997) *Current Biology* 7 : 739-746.

18. Murray WB, Greenhouse PR, Nelson WI, Norman JE, Jeffries DJ, Andreson J. (1991) *Lancet* 338:830-833.

19. Anonymous (1982) Morbidity and Mortality weekly report. Centre for disease control : Atlanta, USA; 31 : 665 - 667.

20. Premanathan M, Rajendran S, Ramanathan T, Kathiresan K, Nakashima H, Yamamoto N. (2000) *Indian J. Med. Res.* 112:73-77.

21. Matthee G, Wright AD, Konig GM. (1999) *Planta Med.* 65:493-506.

22. Vlietinck AJ, De Bruyne T, Apers S, Pieters LA. (1998) *Planta Med.* 64:97-109.

23. Hussein G, Miyashiro H, Nakamura N, Hattori M, Kawahata T, Otake T, Kakinchi N, Shimotohno K. (1999) *Phytother. Res.* 13:31-36.

24. Min BS, Bac KH, Kim YH, Miyashiro H, Hattori M, Shimotohno K. (1998) *Phytother. Res.* 13:680-682.

25. Kim HJ, Woo ER, Shin CG, Park H. (1998) *J. Nat. Prod.* 61:145-148.

26. Hnatyszym O, Broussalis A, Herrera G, Muschietti L, Cousio J, Martino V, Ferraro G, Font M, Monge A, Martinez IJJ. (1999) *Phytother. Res.* 13:206-209.

27. Salomon H, Pampuro S, Cavallaro L, Garcia G, Coussio J, Campos R. (1997) *Phytother Res.* 11:82-83.

28. Xin WY, Jing Z. (1999) *J. Nat. Prod.* 62:1510-1513.

29. Kim HK, Lee HK, Lin CG, Huh H. (1999) *Archives Pharmacol. Res.* 22 : 520-523.

30. Min BS, Hattori M, Lee HK, Kim YH. (1999) *Archives Pharmacol. Res.* 22:75-77.

31. Richard WF, John WB, Jamic LB. (1999) *J. Nat. Prod.* 62:130-132.

32. Hoffman AJ. (1998) *Ayurveda Education Series* 67:44-51.

33. Lagrota MHC, Wigg MD, Santos MMG, Miranda MMFS, Camara FP, Conceiro JNSS. Costa SS. (1994) *Phytother Res.* 8:358-361.

34. Thomas AL, Carpenter BLA. (1995) *J. Herbs Spices Med. Plant* 3:51-54.

35. Thomas DW, Boyd MR, Cordellina JH. (1994) *Economy Botany* 48:413.

36. Calabresc C, Berman SH, Babish JG, Max, Shinto L, Dorr M, Wells K, Wenner CA, Standish LJ. (2000) *Phytother Res.* 14:334.

37. Yang, CW, Yu CH, Fan RC, Mark C, Hui KW. (1996) *J. Nat. Prod.* 59:635-637.

38. Rimando AM, Pezzuto JM, Farnsworth NR, Santisuk T, Rentrakul V, Kawanishi K. (1994) *J. Nat. Prod.* 57:896-904.

39. Sattar EA, Galal AM, Mossa GS. (1996) *J. Nat. Prod.* 59:403-405.

40. Sonia P, Cosimo P, Nunziatina DT, Naheed M. (1996) *J. Nat. Prod.* 59:565-569.

41. Martinotti E, Carderone V, Breschi MC, Bandini P, Cioni PL. (1997) *Phytother Res* . 11 : 612 - 614.

42. Calderone V, Nicoletti E, Baindecchi P, Pistello M, Mazzetti P, Martinotti E, Morelli I. (1998) *Phytother. Res.* 12:595-597.

43. Weibo L. Ruixing W, Chongfen G, Yizhe W, Shao J, Mshiu E, Mbena E. (1995) *Chinese Med. J.* 108:634-637.

44. Min BS, Base K, Kim YH, Shimotohno K, Miyashiro H, Hattori M. (1998) *Nat. Prod. Sciences* 4 : 241-244.

45. Abdel MS, Bastien JW, Mahler WF, Jia Q, Reinecke MG, Robinson WE, Shu YH, Zalles AJ. (1996) *J. Ethnopharmacol.* 50 : 157-166.

46. Galinis DL, Fuller RW, Mcker TC, Cardellina JH, Gulakowski RJ, McMohan JB, Boyd MR. (1996) *J. Med. Chem.* 39:4507-4510.

47. Mathee G, Right AD, Konig GM. (1999) *Planta Med.* 65:493-506.

48. Spino C, Dodier M, Sotheeswaran S. (1998) *Bioorganic Med. Chem. Letters* 8: 3475-3478.

49. Lin YM, Anderson HM, Jenta TR, Willians MJ, Flavin MT, Xu ZQ. (1999) *Pharm Biol.* 37 : 71-76.

50. Dharmaratne HRW, Wanigasekera WMA, Mata GE, Pezznto JM. (1998) *Planta Med.* 64 : 460-461.

51. Sukumar E, Hamsaveni GR, Bhima RR, Vishwanathan S, Thirugnanasambantham P, Vijaysekaran V. (1995) *Fitoterapia* 66 : 403-406.

52. Matsuse IT, Lim YA, Hattori M, Correa M, Gupta MP. (1999) *J. Ethnopharmacol* 64 : 15-22.

53. Hu CQ, Chen K, Shi Q. Killskic RE, Cheng YC, Lee KH. (1994) *J. Nat. Prod.* 57 : 42-51.

54. Ganzera M, Scholz D, Haksche H, Stuppner H. (1996) *Phytomedicine* 3:179.

55. Dai JR, Decosterd LA, Gustafson KR, Cardellina JH, Gray GN, Boyd MR. (1994) *J. Nat. Prod.* 57 : 1511-1516.

56. Min BS, Jung HJ, Lee JS, Kim YH, Bok SH, Ma CM, Nakamura N, Hattori M, Bae KI. (1999) *Planta Med.* 64:374-375.

57. El-Mekkawy S, Meselly MR, Nakamura N, Hattori M, Kawahata MR, Otake T. (2000) *Phytochemistry* 53 : 457-464.

58. Amouroux P, Jean D, Lamaison JL. (1998) *Phytother Res.* 12:367-368.

59. Srimal RC. (1997) *Fitoterapia* 68:483-493.

60. Dc TN, Dc SF, Pizz C, Mahmood N. (1996) *J. Nat. Prod.* 59 : 267-270.

61. Hara H, Maruyama N, Yamashita S, Hayashi Y, Lee KH, Bastow KF, Marumoto R, Imakura Y. (1997) *Chem. Pharm. Bulletin* 45 : 1714-1716.

62. Wafo P, Nyassee B, Fontaine C. (1999) *Phytochemistry* ;50:279-281.

63. Yu YB, Park JC, Lee JH, Kim GE, Jo SK, Byn MW, Miyashiro H, Hattori M. (1998) *Korean J. Pharmacog.* ; 29:338-346.

64. Matsuse IT, Lim YA, Hattori M, Correa M, Gupta MP. (1997) *International Joint symposium for Chemical, Biological and Pharmaceutical properties of Medicinal Plants from the Americas*, February 23 - 26, Republic of Panama; Panama : B-2.

65. Zheng WF, Cui Z, Zhu Q. (1998) *Planta Med.* 64 : 754-756.

66. Ross SA, El SKA El SMA, Humann MT, Abdel HOB, Ahmed AF, Ahmed MM. (1997) *Plant Med.* 63:479-482.

67. Hong XX, Fa QZ, Min W, Keng YW. (1996) *J. Nat. Prod.* 59 : 643-645.

68. Konoshima T, Yasuda I, Kashiwada Y, Cosentino LM, Lee KH. (1995) *J. Nat. Prod.* 58 : 1372-1377.

69. Sivkumar R, Nair AGR, Madhusudhanam KP. (1995) *Current Sci.* 69 : 23-24.

70. Alan CP. (1994) *Fourth Int Cong Ethnobiol*, Nov. 17-21, NBRI Lucknow, India :170.

71. Hayashi K, Kamiya M, Hayashi T. (1995) *Plant Med.* 61:237-241.

72. Sokmen A, Jones BM, Erturk M. (1999) *Phytother Res.* 13:355-357.

73. Kashiwada Y, Wang HK, Nagao T, Kitanaka S, Yasuda I, Gujioka T, Yamagishi T, Cosentino

LM, Kozuka M, Okabe H. (1998) *J. Nat. Prod.* 61:1090-1095.

74. Kavimani S, Jaykar B, Clearcq ED, Panecouque C, Witvrouw M. (1998) *Hamdard Medicus.* 43:5-7.

75. Muanza DN, Euler KL, Williams L, Newman DJ. (1998) *Int. J. Pharmcog.* 33:98-106.

76. Chen DF, Zhang SX, Chen K, Zhon BN, Wang P, Cosentino LM, Lee KH. (1996) *J. Nat. Prod.* 59 : 1066-1068.

77. Dao F, Shun XZ, Hui KW, Shi YZ, Quan ZS, Cosentino LM, Kuo HL. (1999) *J. Nat. Prod.* 62:94-97.

78. Zhihong X, Fang RC, Hai KW, Yoshiki K, Andrew TM, Kenneth FB, Yoko T, Mark C, KuOH. (2000) *J. Nat. Prod.* 63 : 1712-1715.

79 . Hallock YF, Sowder II RC, Pannell LK, Hughes CB, Johnson DG, Gulakowski R, Cardellina JH, Boyd MR. (2000) *J. Org. Chem.* 65 : 124-128.

80. Yamasaki K, Otake T, Mori H, Morimoto M, Ueba N, Kurokawa Y, Shiota K, Yuge T. (1993) *Yakugaku Zasshi* 113:818-824.

81. Amiram G, John HC, Michal RB. (2000) *J. Nat. Prod.* 63:1537-1539.

82. Pengsuparp T, Cai L, Fong HHS, Kinghorn AD, Pezzuto JM, Wani MC, Wall ME. (1994) *J. Nat. Prod.* 57:415-418.

83. Beutler JA, Kashman Y, Tischler M, Cardellina JH, Gray GN, Currens MJ, Wali ME, Wani MC, Boyd MR. (1995) *J. Nat. Prod.* 58:1039-1046.

84. Dc TN, Pincerte S, Rastrclli L, Mahmood N, Pizza C. (1998) *Pharm. Biol.* 36 : 29-32.

85. Hussein G, Nakamura N, Meselhy MR, Hattori M. (1999) *Phytochemistry* 50 : 689-694.

86. Yamamoto T, Takahashi H, Sakai K, Kowithayakorn T, Koyano T. (1997) *Nat. Med.* 51:541-546.

87. Ramanathan T, Premanathan M, Kathiresan K, Nakashima H, Yamamoto N. (1999) *South East Asian Seminar on Herbs and Herbal Medicines.* January 16 - 19 : Patna; Jan 16-19 :125.

88. Hasegawa H, Matsumiya S, Uchiyama M, Kurokawa T, Inouge Y, Kasai R, Ishibashi S, Yamasaki K. (1994) *Planta Med.* 60 : 240-243.

89. Nishibe S, Ono K, Nakane H, Kawamura T, Noro Y, Tanaka T. (1997) *Nat. Med.* 51 : 547-549.

90. El MS, Meselhy MR, Kusumoto IT, Kadota S, Hattori M, Namba T. (1995) *Chem. Pharm. Bull.* 43 : 641-648.

91. Paris A, Strukclj B, Renko M, Turk V, Puki M, Umek A, Korant BD. (1993) *J. Nat. Prod.* 56 : 1426-1430.

92. Girbes T, Citores L, Ferreras JM, Rojo MA, Iglesias R, Munoz R, Arias FJ, Calonge M, Garcia JR, Mendez E. (1993) *Plant Molecular Biol.* 26 : 1181-1186.

93. Han DS, Sheng XQ, Long ZL, Zong W, Zhong WL, Thitima P, John MP, Harry HSF. (1996) *J. Nat. Prod.* 59:525-527.

94. Niyonzima G, Lackeman G, Witvrouw M, Van PB, Pieters L, Paper D, De CE, Franz G, Vlietinck AJ. (1999) *Phytomed.* 6 : 45-49.

95. Gujioka T, Kashiwada Y, Kikishie RE, Cosentino LM, Ballas LM, Jiang JB, Janzen WP, Chen IS, Lee KH. (1994) *J. Nat. Prod.* 57 : 243-247.

96. Mohibb A, Ghanim MA. (2000) *Annals. Arid. Zone* 39 : 93-95.

97. Valsaraj R, Pushpangdan P, Smitt UW, Adsersen A, Christensen SB, Sittie A, Nyman U, Nielsen C, Olsen CE. (1997) *J. Nat. Prod.* 60 : 739-742.

98. Rashdi MA, Gustafson KR, Kashman Y, Cardellina II JH, McMohan JB, Boyd MR. (1995) *Nat. Prod. Letters* 6 : 153-156.

99. Ishikawa T, Kotake K, Shii H. (1995) *Chem. Pharm. Bulletin* 43 : 1039-1041.

100. Hongquan D, Yoshihisa T, Yashuhiro I, Yongfong J, Duan L, Mark C, Kuo HL. (2000) *J. Nat. Prod.* 63 : 357-361.

101. Richard WF, Chandra KW, Joseph WC. (1999) *J. Nat. Prod.* 62 : 67-69.

102. Piacente S, Aquino R, Dc TN, Pizz C, De VL, Orellana HC, Mahmood N. (1994) *Phytochemistry* 36 : 991-996.

103. Chao MM, Norio N, Masao H, Hiroko K, Jun CQ, Hai LY. (2000) *J. Nat. Prod.* 63 : 238-242.

104. Hertzberg RP, Johnson RK, Caranaga MJ, Myers CC, Mackenzic L. (1992) In: Coombes JD. (ed.) *New drugs from natural sources.* London : IBC Technical Services Ltd.

105. Chang RS, Smith KM. (1989) *Antiviral Res.* 11 (5-6) : 263-273.

106. Yao XJ, Wainberg MA, Parnials MA. (1992) *Virology.* 187(1) : 56-62.