*Proceedings of theWorkshop on Medicinal Plants of Bangladesh, 1-12, 2006*

# Terpenoids from *Curcuma* species

*Myint Myint Khine, Norbert Arnold, Katrin Franke , Ludger A. Wessjohann**
Leibniz Institute of Plant Biochemistry, Dept. Bioorganic Chemistry
Weinberg 3, D-06120 Halle (Saale), Germany
Fax: ++49 (345) 5582-1309; wessjohann@ipb-halle.de

## Abstract

The article very briefly reviews some general aspects of drug development from natural products, then concentrates on the phylogeny of *Curcuma* within the Zingiberaceae, followed by a short review of *Curcuma* constituents. Finally an emphasis is placed on *Curcuma comosa*, native to Bangladesh, Myanmar and related areas, highlighting new results, especially from the authors lab.

## Introduction

### Natural Products and Drug Discovery

Plants are the basis for traditional medicine for thousands of years, with the first records dating from around 2600 BC in Mesopotamia. They used oils from cedar and cypress, licorice, myrrh, and poppy juice, among other things - substances that are still in use today for the treatment of various illnesses and infections. Ancient Arab, Indian, and Chinese documents show that medicine in these societies included numerous plant-based remedies and preventives. The Greeks and Arabs both contributed substantially to the assimilation, codification, and development of plant-based medicines, like the Unani-medicine valuated, e.g., in Bangladesh. The isolation of the active principles from the plants and herbs such as strychnine, morphine, and colchicine began in the early 1800s. [Newman *et al.*, 2000; Newman & Cragg, 2007].

Today approximately 70 percent of the world's population relies on traditional plant-based medicines for primary health care. But also the remaining 30 percent of the world's population depend to a considerable extent on plant products for health care. Germany now is recognized for the most advanced phytomedicinal industry. About 25 percent of prescription drugs dispensed in the United States contain plant extracts or active ingredients derived from plants. Out of a total of 1184 new chemical entities between 1981 and 2006, 59 (5%) were natural products, 272 (23 %) derived natural products, and 166 (14 %) biological origin (peptides or proteins isolated from organism or cell lines). Additional 201 (17 %) compounds, were chemicals either made by total synthesis (59, 5 %), but the pharmacophore is/was found from a natural product or mimics a natural product (142, 12 %). [Newman *et al.*, 2000 ; Wessjohann *et al.* 2005 ; Newman & Cragg, 2007].

Despite the great successes already achieved in natural products chemistry and drug development, the potential of natural molecular diversity is barely tapped. Only some 15 percent of the 250,000 species of higher terrestrial plants have been chemically and pharmacologically investigated in a more or less systematic fashion. The percentage of insects, marine organisms, fungi and microbes investigated is even lower. In the case of fungi, it is estimated that 90 % of existing species are currently not even known, never mind analyzed. There is currently great interest in exploring extreme habitats [http://www.aaas.org/international/africa/gbdi/mod1b.html] for useful compounds and enzymes from microbes, including acidophiles (from acidic sulfurous hot springs), alkalophiles (from alkaline lakes), halophiles (from salt lakes), thermophiles (from deep sea vents), and psychrophiles (from extremely cold waters), or from within organismsm (e.g. endophytic fungi). Also, most scientists still tend to learn from structures only, but learning from natures ways and systems, e.g. for synthesis, drug-stabilization, delivery, or resistance avoidance may be even more rewarding. [Wessjohann *et al.* 2005]

In todays industry, systematic approaches are used. High-throughput screening allows to test hundreds of potential targets with thousands of diverse chemical compounds in order to identify a promising lead compounds (chemical entities that interact with targets and therefore have potential as drugs). The alternative method of rational drug design involves the (computational) analysis, design and synthesis of compounds based either on the known structure of either a specific target or on its (natural) ligands and effectors . The results of the Human Genome Project and human pathogen genome projects provide many new potential drug targets. For this reason, target identification must be followed by target validation, which confirms the likelihood that interfering with the target protein will impact on the disease. However, these biochemical and

rational processes often lack a "system" tolarability, i.e. many have an excellent performance on a receptor or enzyme and fail in the whole organism. Thus whole cell or even organism based assays under have become valuable again, in addition or prior to biochemical assays. This is most evident in chemical genomics approaches.

The development of a new therapeutic drug following the western standard for single compound drug development is complex, lengthy and very expensive. It can take from 10-15 years and over € 800 Mio to bring a drug from concept/isolation to market. This includes the increasingly costly phases of pre-clinical and clinical development and additional time for dealing with the regulatory authorities (Figure 1). Although in many countries exceptional rules apply for plant extracts with a previous human use history, also their legislation and marketing requires several million Euros.

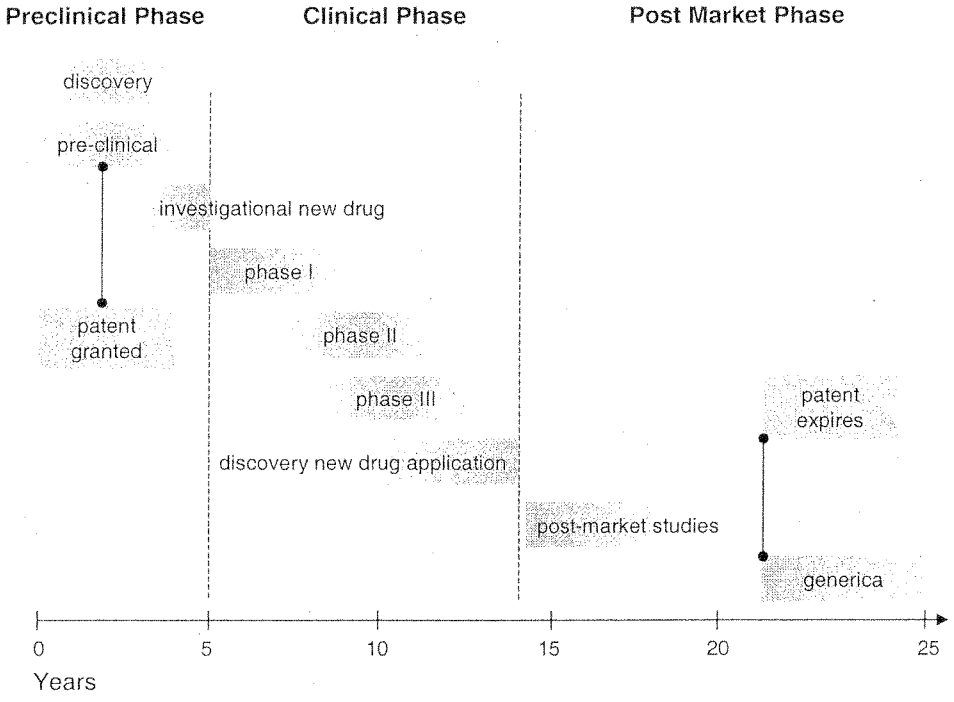



**Figure 1. The development of a new therapeutic drug**

## Phylogeny of the Zingiberaceae

The pantropical Zingiberaceae is the largest family in the order Zingiberales with 53 genera and over 1200 species. Classifications of the family, first proposed in 1889 [Petersen, 1889] and refined by others since that time, recognize four tribes (Globbeae, Hedychieae, Alpinieae, and Zingibereae) based on morphological features.

New phylogenetic analyses are based on DNA sequences of the nuclear internal transcribed spacer (ITS) and plastid *matK* regions. This research suggests that at least some of these morphological traits are homoplasious and three of the tribes are paraphyletic. The African genus *Siphonochilus* and Bornean genus *Tamijia* are basal clades. The former Alpinieae and Hedychieae for the most part are monophyletic taxa with the Globbeae and Zingibereae included within the latter. A new classification of the Zingiberaceae that recognizes four subfamilies and four tribes: Siphonochiloideae (Siphonochileae), Tamijioideae (Tamijieae), Alpinioideae (Alpinieae, Riedelieae), and Zingiberoideae (Zingibereae, Globbeae) was recently suggested [figure 2 from: Kress *et al.*, 2002].

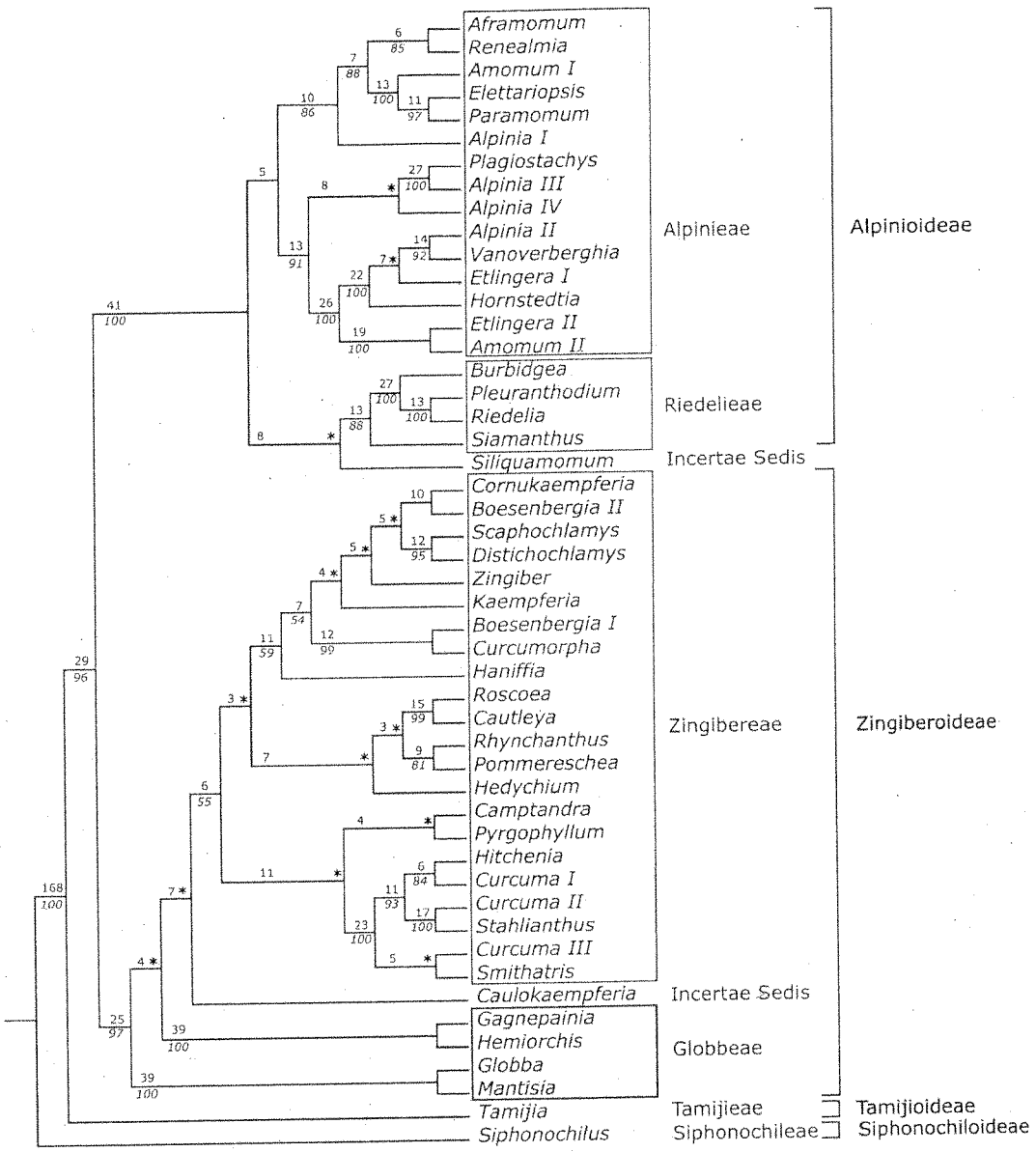



**Figure 2. Phylogenetic tree of Zingiberaceae [*Kress et al., 2002].***

## Botanical description of *Curcuma comosa* Roxb.

*Curcuma comosa* belongs to the subfamily Zingiberoidae of the Zingiberaceae family. The genus *Curcuma* has 80 species. More than 50 species have been found in Thailand and 24 species are widely spread in Myanmar and neighboring countries like Bangladesh [http://www.iupac.org/symposia/proceedings/phuket97/sirirugsa.pdf; Kress *et al.*, 2003]. The botanical description of *Curcuma* species is as follow:

Rootstock large of palmately branched sessile annulate tuber, aromatic with light yellow circling deeper yellow inside when young; colour changing to bright orange on becoming older. Leaves large, lanceolate to oblong-elliptic, leaf-stalk as long as the blade, plain green except in the earliest, which are clouded with faint brown down the centre above, glabrous on both sides. Flowering spike arising from the centre of the tuft of leaves. Appearing after the leaves are developed, flowers fragrant, pinkish-yellow, longer than the flowering bracts; flower bracts greenish tipped with purplish-red streak, those of the coma tinged with purplish-red at the tip and with white base below. Family Zingiberaceae. Flowering in late August to September [http://www.tuninst.net/MyanMedPlants/DMB-USG/hypoten/hypo.htm#Curcuma-Comosa].

## IMPORTANCE OF THE GENUS *CURCUMA*

The significance of *Curcuma* in health and nutrition has been recognized since the discovery of the antioxidant properties of naturally occurring phenolic compounds, mostly the so called curcuminoids [Jayaprakasha *et al.*, 2002; Lechtenberg *et al.*, 2004; Srinivasan, 1953]. The important curcuminoids of turmeric, especially from the turmeric plant *C. longa*, are processed in the rhizome and are used as spice, herbal medicine, dyeing agent and cosmetic since Vedic age [Salvi et al, 2000; Shirgurkar *et al.*, 2001; Majeed *et al.*, 1995] .

So far, a number of different biologically active compounds have been isolated from various *Curcuma* species demonstrating germicidal, aromatic, carminative, antihelmintic, antioxidant anti-tumor, cholesterol lowering, and neuroprotective properties [Cao *et al.*, 2001; Cao & Komatsu, 2003; Jitoe *et al.*, 1992; Joe *et al.*, 2004; Kikuzaki & Nakatani, 1993; Majeed *et al.*, 1995; Masuda *et al.*, 1993; Sasaki *et al.*,2002; Sasaki *et al.*, 2004; Purseglove, 1974]. Especially in the traditional Asian medicine these drugs were used to treat various syndromes due to obstruction of blood circulation, retention of blood stasis (e.g. anthralgia, psychataxia, dysmennorrhea), for dyspepsia, and for itching and infected wounds. [Cao *et al.*, 2001 ; Sasaki *et al.*, 2002 ; Saralamp *et al.*, 1996]. The effectiveness for treatment of dyspepsia, peptic ulcers and gastric ulcers could be demonstrated [Masuda *et al.*, 1993].

### Pharmacological activities of principal constituents from *Curcuma* species

Sesquiterpenoids and phenolic diarylheptanoids are major constituents in turmeric (*Curcuma*). Curcumin (**1**) and its analogues show many biological activities, including cytotoxicity [Aggarwal *et al.*, 2003], nematocidal activity [Kiuchi *et al.*, 1993], anticancer activity [Simon *et al.*, 1998], topoisomerase inhibition [Roth *et al.*, 1998], antioxidant activity [Soudamini *et al.*, 1992], protection against alcohol induced liver toxicity [Rajakrishnan *et al.*, 1998], antimalaria activity against *Plasmodium falciparum* and *Leishmania major* [Rasmussen *et al.*, 2000].

Several synthetic curcumin analogues also showed potent antiandrogenic activities against two human prostate cancer cell lines, PC-3 and DU-145, and were superior to hydroxyl flutamide, which is the currently available antiandrogen for the treatment of prostate cancer [Ohtsu *et al.*, 2002]. This new class of antiandrogen agents could be developed into clinical trial candidates to control antiandrogen receptor-mediated prostate cancer growth [Lee, 2004].

1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (**2**), and procurcumenol (**3**) inhibit the production of TNF-α by lipopolysaccharide (LPS) activated macrophages ($IC_{50}$ 12.3 and 310.5 μM) [Jang *et al.*, 2001]. The 80% acetone extract of *Zedoariae* Rhizome showed vasorelaxant [Yoshikawa *et al.*, 1998], hepatoprotective [Matsuda *et al.*, 1998, 2001c], and nitric oxide production inhibitory activities [Matsuda *et al.*, 2001d]. Germacrone (**4**) ($IC_{50}$ 19 μM), isocurcumenol (**5**) (26 μM), *β*-eudesmol (**6**) (16 μM), and *β*-dictyopterol (**7**) (9 μM) show potent vasorelaxant effects [Matsuda *et al.*, 2001a]. The effect of isolated constituents from Zedoariae rhizome on NO production from LPS-activated macrophages was examined by Matsuda H *et al.* [Matsuda *et al.*, 2001b]. Gajustulactones A (**8**), B (**9**), curcumenone (**10**), furanodiene (**11**), isofuranodienone (**12**), 13-hydroxygermacrone (**13**), glechomanolide (**14**), neocurdione (**15**), curcumenol (**16**), isocurcumenol (**5**), procurcumenol (**3**), curcumin (**1**) and bis(4-hydroxycinnamoyl)methane (**17**) were found to inhibit NO production ($IC_{50}$ 13 μM-93 μM) [Matsuda *et al.*, 2001b]. Principal sesquiterpenes, furanodiene (**11**), germacrone (**4**), curdione (**18**), neocurdione (**15**), curcumenol (**16**), isocurcumenol (**5**), aerugidiol (**19**), zedoarondiol (**20**), curcumenone (**10**) and curcumin (**1**) also show potent protective effect on D-galactosamine/lipopolysaccharide-induced acute liver injury in mice [Matsuda *et al.*, 1998].

## SECONDARY METABOLITES FROM *CURCUMA* SPECIES

### *Curcuma aromatica* Salisb.

Rhizomes of *C. aromatica*, are used as oriental traditional medicines in China, Japan and Southeast Asia. From these plants, many kinds of sesquiterpenes have been isolated. In 1987, three new sesquiterpenes, isozedoarondiol, methylzedoarondiol and neocurdione, were isolated along with seven known sesquiterpenes, germacrone (**4**), curdione (**18**), (4*S*,5*S*)-germacrone 4,5-epoxide (**21**), dehydrocurdione (**22**), procurcumenol

(**3**), zedoarondiol (**20**) and curcumenone (**10**) from rhizomes of *C. aromatica* [Kuroyanagi *et al.*, 1987; Giang & Son, 2002]. In 1990, further study on the sesquiterpenes has carried out to give eleven minor sesquiterpenes, having guaiane, seco-guaiane and germacrane skeletons [Kuroyanagi *et al.*, 1990].

***Curcuma heyneana*** Val. & V. Zijp

*C. heyneana* is one of the zingiberaceous plants indigenous to Java Island, Indonesia. The rhizome of this plant is of wide medicinal value in Indonesia, and is considered to be useful for the treatment of skin diseases, abrasions and injuries. A new guaiane sesquiterpene, oxycurcumenol (**23**), together with known sesquiterpenes germacrone (**4**), dehydrocurdione (**22**), isocurcumenol (**5**), curcumenol (**16**), curcumanolide A (**24**), B (**25**) and zerumbone (**26**) were isolated [Firman *et al.*, 1988].

***Curcuma wenyujin*** **Y.H Cheng & C. Ling.**

*Curcuma wenyujin* is currently used as a clinical remedy for uterus cancer in China. Sesquiterpenes possessing a 7α-isopropyl group, such as curcumol (**27**), curdione (**18**), curcumalactone (**28**), and a new epoxy germacrane, (1*R*,10*R*)-epoxy-(−)-1,10-dihydrocurdione (**21**), were isolated from the essential oil. Other sesquiterpenes, neocurdione and (1*S*,10*S*),(4*S*,5*S*)-germacrone-1(10), 4-diepoxide (**30**) were also isolated from this plant [Harimaya *et al.*, 1991; Inayama *et al.*, 1985]

***Curcuma longa*** **Salisb.**

The rhizome of *C. longa* is also used as a yellow colouring food additive, because it contains curcuminoids. From the rhizomes of this plant, curcuminoids and five new sesquiterpenes, germacrone-13-al, 4-hydroxybisabola-2,10-diene-9-one (**31**), 4-methoxy-5-hydroxy-bisabola-2,10-diene-9-one (**32**), 2,5-dihydroxybisabola-3,10-diene (**33**), and procurcumadiol (**34**) were isolated along with curcumenone (**10**), dehydrocurdione (**22**), (4S,5S)-germacrone-4,5-epoxide (**29**), bisabola-3,10-diene-2-one (**35**), α-turmerone (**36**), bisacumol (**37**), bisacurone (**38**), curcumenol (**16**), isoprocurcumenol (**39**), zedoarondiol (**20**), and procurcumenol (**3**) [Ohshiro *et al.*, 1990; Li *et al.*,2003].

***Curcuma zedoaria*** **Roscoe (syn. *C. aeruginosa* Roxb.)**

The crude drug zedoary, the dried and ground rhizome of *C. zedoaria*, has been used medicinally in China. In Japan, it has also been used medicinally, mainly as an aromatic stomachic. The rhizome of *C. zedoaria* is also widely used as a stimulant, stomachic, carminative, diuretic, anti-diarrheal, anti-emetic, anti-pyretic, anti-inflammatory and depurator in India and Southeast Asia countries. As it contains bioactive principles, the constituents of zedoary have been investigated extensively and it is recognized to be a rich source of terpenoids. Until now, 3 major curcuminoids and over 40 sesquiterpenes, belonging to eudesmane type, guaiane type, carabrane type, germacrane type, bisaborane type, elemane type, and xanthane type have been isolated from this plant. Some sesquiterpenoids obtained from *C. zedoaria* are: the cyclopropanosesquiterpene curcumenone (**10**), curcarabranols A (**40**) and B (**41**), curcumenolactones A (**42**), B (**43**) and C (**44**), 4-epicurcumenol (**45**), neocurcumenol (**46**), gajutsulactones A (**8**) and B (**9**), and zedoarolides A (**47**) and B (**48**) [Matsuda *et al.*,. 2001a; Matsuda *et al.*,. 2001b; Jang *et al.*, 2001; Shiobara *et al.*, 1985; Takano *et al.*, 1995; Shibuya *et al.*, 1987; Hikino *et al.*, 1966, 1968,1971; Kouno *et al.*, 1985].

***Curcuma comosa*** **Roxb. – including new results from the Wessjohann group**

The rhizomes of *Curcuma comosa* Roxb. have been used extensively in indigenous medicine in Thailand as an anti-inflammatory agent. It has also been used to reduce malaria fever by combining it with *Artemisia annua* and *Aristolochia tagala* by Myanmar practitioners and as an aromatic stomachic. In 1994, the inhibition of the motility of the nematode *Caenorbabditis elegans* was tested and five diphenylheptenoids were isolated as a consequence [Jurgens *et al.*, 1994]. In 1997, three known diarylheptanoids, 1,7-diphenyl-5-hydroxy-(1*E*)-1-heptene (**49**), 5-hydroxy-7-(4-hydroxyphenyl)-1-phenyl-(1*E*)-1-heptene (**50**) and 7-(3,4-dihydroxyphenyl)-5-hydroxy-1-phenyl-(1*E*)-1-heptene (**51**), and a phloracetophenone glucoside (**52**) were described [Suksamrarn *et al.*, 1997].

Recently, our group could isolate several curcuminoids and sesquiterpenoids (compounds **1, 3, 5, 9, 10, 16, 18, 20, 30, 37, 39, 48, 53 - 69** Table 1) including nine new sesquiterpenes (**54 - 56, 58, 60, 61, 63 - 66**) from

the rhizome of *Curcuma comosa*. One of these (**69**) was previously only known from *Zingiber officinale* [Kikuzaki *et al.*, 1991]

In a screening program some of the sesquiterpenes isolated from *Curcuma comosa* (compounds **30, 48, 53, 56, 59, 62, 60**) were tested for their cellular viability in the human leukemic cell U937 () at concentrations of 100 μM, 10 μM, and 1 μM. Only compound **30** [(1S, 10S), (4S, 5S)-germacrone-1(10), 4(5)-diepoxide] showed the induction of apoptosis (viability % 71.60) at 100 μM.

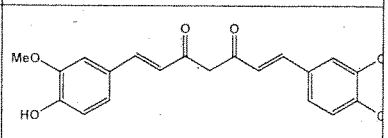
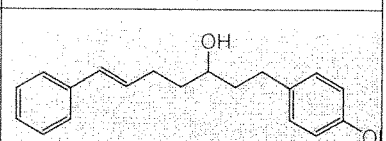
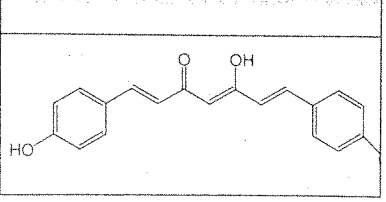
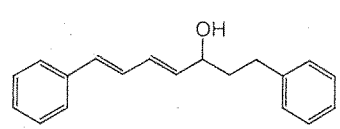
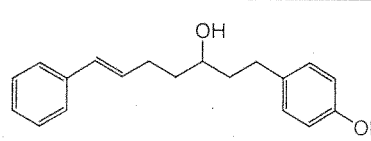
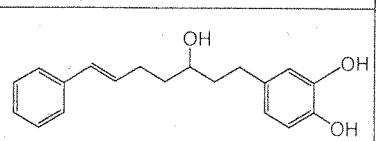
Crude extracts from rhizomes of *Curcuma comosa* (*n*-hexane, ethyl acetate, *n*-butanol, water) and curcuminoids (**1,67, 68**) were also tested for their fungicidal properties against the phytopathogenic fungi *Cladosporium cucumerinum* according to the semiquantitative method described by Gottstein *et. al.* (1982). The tested curcuminoids showed antifungal activity below 20 μg while the tested crude extracts exhibited only weak activity (Table 2).

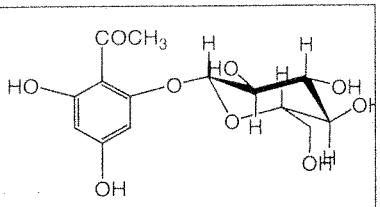
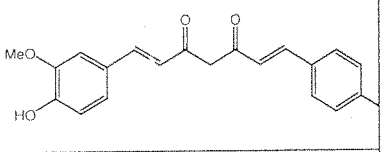
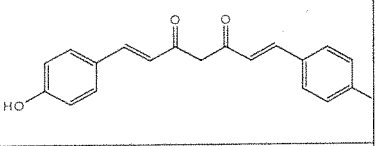
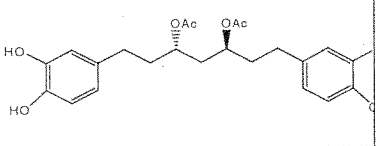
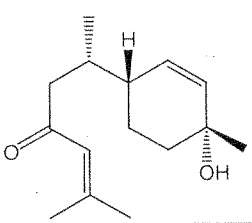
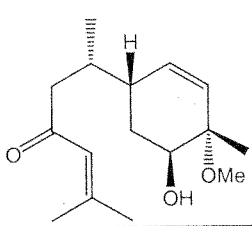
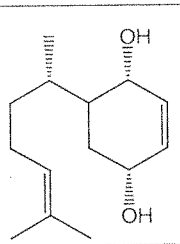
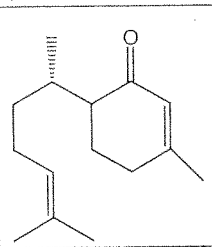
Overall, the potential of the tested extracts and curcuminoids as antifungal and anticancer compounds appears to be quite limited.

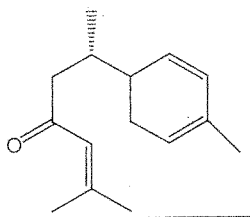
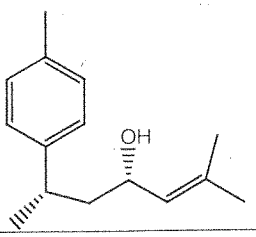
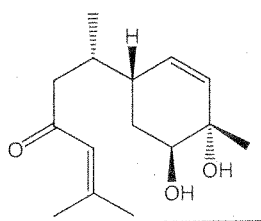
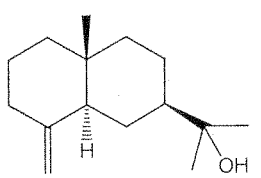
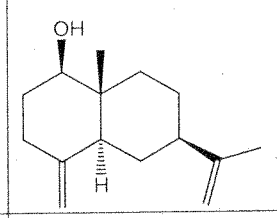
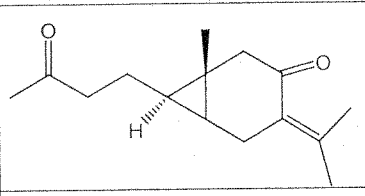
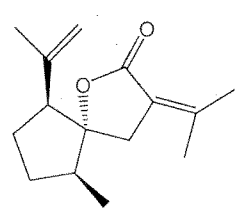
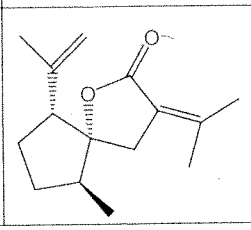
**Table 2. Inhibition zones in mm$^2$ of antifungal activity of curcuminoids (1, 67, 68) and crude extracts from *C. comosa*.**

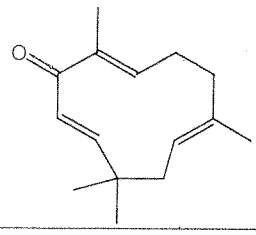
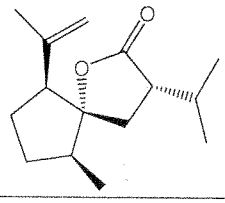
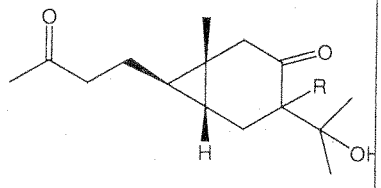
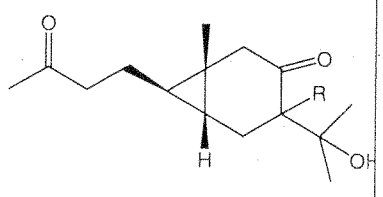
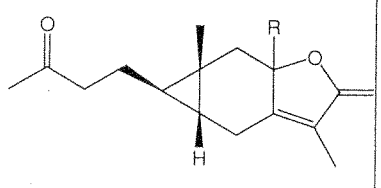
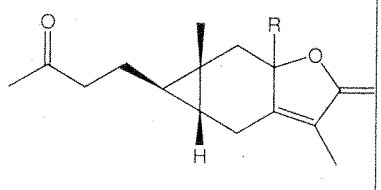
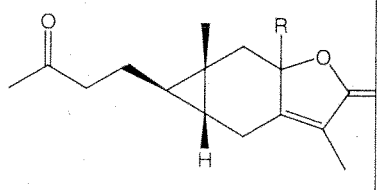
| | *C. comosa* crude extract | | *C. comosa* pure compounds |
|---|---|---|---|
| | 250 μg | 250 μg | 20 μg |
| *n*-hexane | 154 | 227 | - |
| ethylacetate | 113 | 154 | - |
| *n*-butanol | 64 | 95 | - |
| water | - | - | - |
| **1, 67, 68** | - | - | 154 |

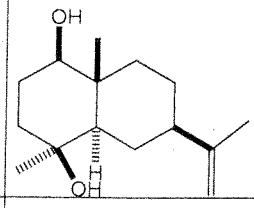
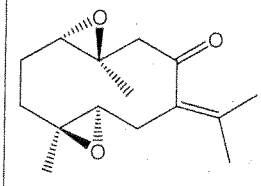
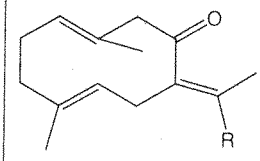
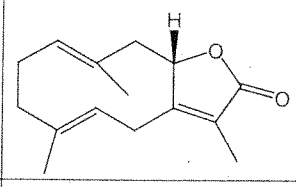
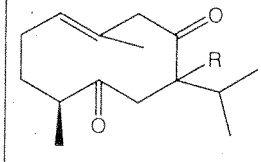
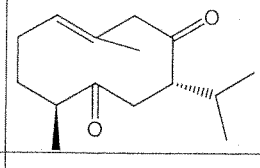
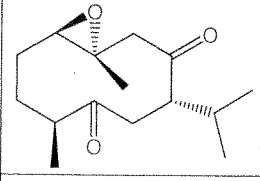
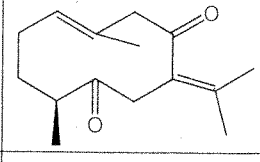
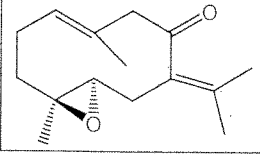
**Table 2. List of compounds from *Curcuma* spp.**

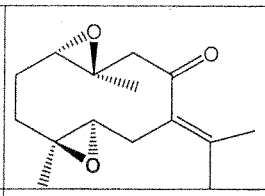
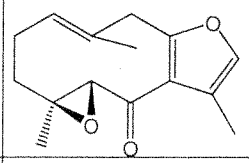
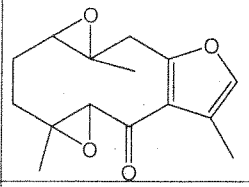
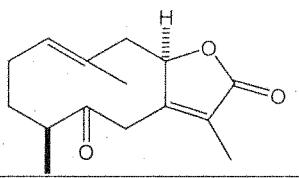
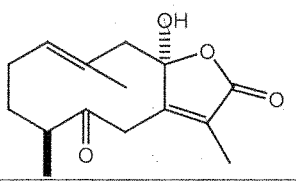
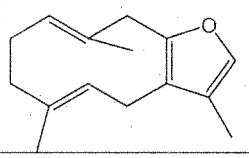
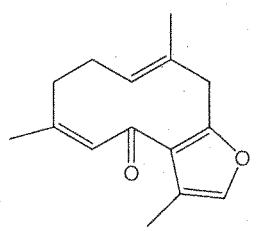
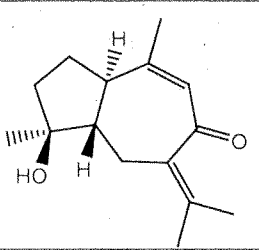
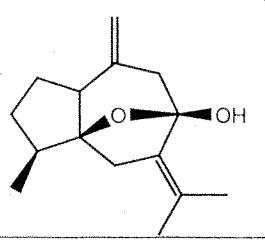
| Class of compound | | Structure |
|---|---|---|
| Diarylheptanoids | 1 |  |
| Diarylheptanoids | 2 |  |
| Diarylheptanoids | 17 |  |
| Diarylheptanoids | 49 |  |
| Diarylheptanoids | 50 |  |
| Diarylheptanoids | 51 |  |

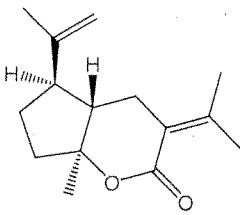
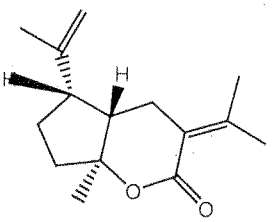
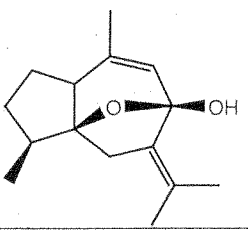
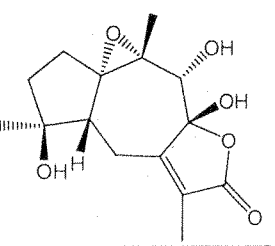
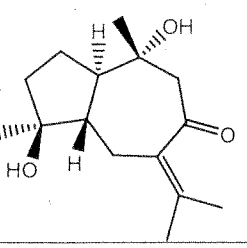
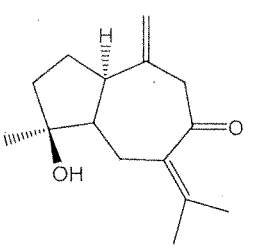
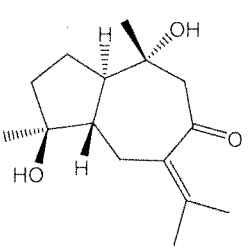
| | | |
|---|---|---|
| Diarylheptanoids | 52 |  |
| Diarylheptanoids | 67 |  |
| Diarylheptanoids | 68 |  |
| Diarylheptanoids | 69 |  |
| Bisaborane typ | 31 |  |
| Bisaborane typ | 32 |  |
| Bisaborane typ | 33 |  |
| Bisaborane typ | 35 |  |

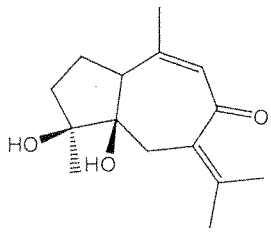
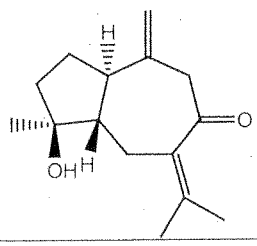
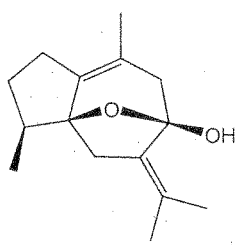
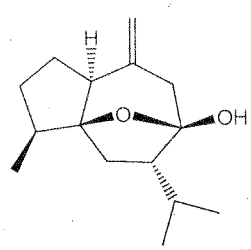
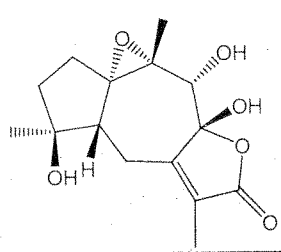
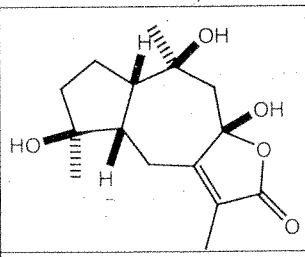
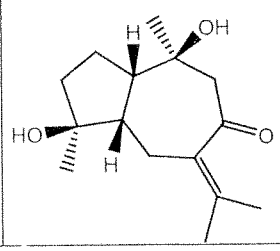
| | | |
|---|---|---|
| Bisaborane typ | 36 |  |
| Bisaborane typ | 37 |  |
| Bisaborane typ | 38 |  |
| Carabrane type | 6 |  |
| Carabrane type | 7 |  |
| Carabrane type | 10 |  |
| Carabrane type | 24 |  |
| Carabrane type | 25 |  |

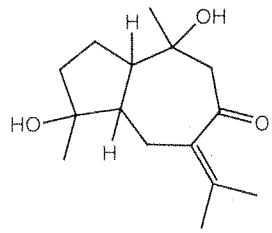
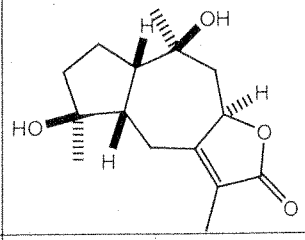
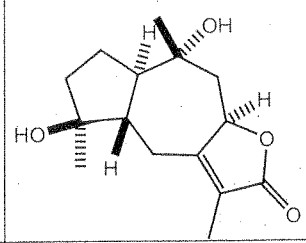
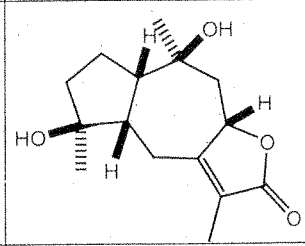
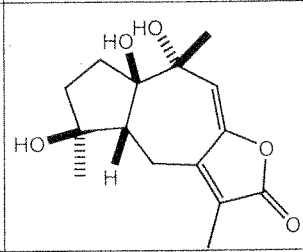
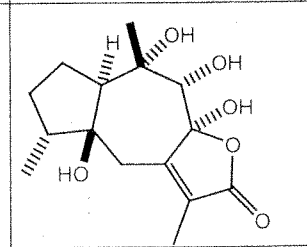
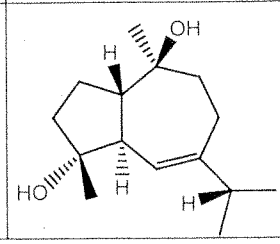
| | | |
|---|---|---|
| Carabrane type | 26 |  |
| Carabrane type | 28 |  |
| Carabrane type | 40 |  R = $\beta$-H |
| Carabrane type | 41 |  R = $\alpha$-H |
| Carabrane type | 42 |  R = $\beta$-H |
| Carabrane type | 43 |  R = $\alpha$-H |
| Carabrane type | 44 |  |

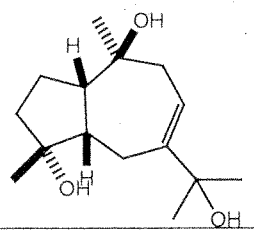
| | | |
|---|---|---|
| | | R = $\alpha$-OH |
| Eudesmane type | 66 |  |
| Germacrane typ | 4 |  R = H |
| Germacrane typ | 13 |  R = $CH_2OH$ |
| Germacrane typ | 14 |  |
| Germacrane typ | 15 |  R = $\alpha$-H |
| Germacrane typ | 18 |  |
| Germacrane typ | 21 |  |
| Germacrane typ | 22 |  |
| Germacrane typ | 29 |  |

| | | |
|---|---|---|
| Germacrane typ | 30 |  |
| Germacrane typ | 53 |  |
| Germacrane typ | 54 |  |
| Germacrane typ | 55 |  |
| Germacrane typ | 56 |  |
| Germacrane type | 11 |  |
| Germacrane type | 12 |  |
| Guaiane type | 3 |  |
| Guaiane type | 5 |  |

| | | |
|---|---|---|
| Guaiane type | 8 |  |
| Guaiane type | 9 |  |
| Guaiane type | 16 |  |
| Guaiane type | 19 |  |
| Guaiane type | 20 |  |
| Guaiane type | 23 |  |
| Guaiane type | 27 |  |

| | | |
|---|---|---|
| Guaiane type | 34 |  |
| Guaiane type | 39 |  |
| Guaiane type | 45 |  |
| Guaiane type | 46 |  |
| Guaiane type | 47 |  |
| Guaiane type | 48 |  |
| Guaiane type | 57 |  |

| | | |
|---|---|---|
| Guaiane type | 58 |  |
| Guaiane type | 59 |  |
| Guaiane type | 60 |  |
| Guaiane type | 61 |  |
| Guaiane type | 62 |  |
| Guaiane type | 63 |  |
| Guaiane type | 64 |  |

| | | |
|---|---|---|
| Guaiane type | 65 |  |



**Acknowledgements**

We thank Morphochem AG / R&D Biopharmaceuticals for tumor cell line assays. Myint Myint Khine thanks the Daimler-Benz Foundation for a Ph.D.-scholarship. Katrin Franke thanks HWP for financial support, and Ludger A. Wessjohann the DAAD for a travel grant to Bangladesh.

**References**

1. Aggarwal, B. B.; Kumar, A.; Bharti. A. C. 2003. Anticancer Res. 23, 363-398.
2. Cao, H.; Komatsu, K. 2003. Yao Xue Xue Bao. 38,871-875.
3. Cao, H.; Sasaki, Y.; Fushimi, H.; Komatsu, K. 2001. Biol. Pharm. Bull 24, 1389-1394.
4. Firman, K.; Kinoshita, T.; Itai, A.; Sankawa, U. 1988. Phytochemistry 27, 3887-3891.
5. Giang, P. M.; Son, P. T. 2002. Journal of Chemistry 40, 108-112.
6. Gottstein, D.; Gross, D.; Lehmann, H. 1982. Arch. Phytopathol. Pfl. 20, 111-116.
7. Harimaya, K.; Gao, J. F.; Ohkura, T.; Kawamata, T.; Iitaka, Y.; Guo, Y. T.; Inayama, S. 1991. Chem. Pharm. Bull. 39, 843-853.
8. Hikino, H.; Konno, C.; Takemoto, T. 1971. Chem. Pharm. Bull. 19, 93-96.
9. Hikino, H.; Sakurai, Y.; Numabe, S.; Takemoto, T. 1968. Chem. Pharm. Bull. 16, 39-42.
10. Hikino, H.; Takahashi, H.; Sakurai, Y.; Takemoto, T.; Bhacca, N. S. 1966. Chem. Pharm. Bull. 14, 550-551.
11. http://www.aaas.org/international/africa/gbdi/mod1b.html. 21.12.2007.
12. http://www.iupac.org/symposia/proceedings/phuket97/sirirugsa.pdf, 24.09.05. 21.12.2007.
13. http://www.tuninst.net/MyanMedPlants/DMB-USG/hypoten/hypo.htm#Curcuma-Comosa, 21.12.2007.
14. Inayama, S.; Gao, J. F.; Harimaya, K.; Hikichi, M.; Iitaka, Y.; Guo, Y. T.; Kawamata, T. 1985. Chem. Pharm. Bull. 33, 2179-2182.
15. Jang, M. K.; Sohn, D. H.; Ryu, J. H. 2001. Planta Med. 67, 550-552.
16. Jayaprakasha, G.K.; Rao, L.J.M.; Sakariah, K.K. 2002. J. Agr. Food. Chem. 50, 3668-3672.
17. Jitoe, A.; Masuda, T.; Tengah, I.G.P.; Suprapta, D. N.; Gara, I. W.; Nakatani, N. 1992. J. Agr. Food Chem. 40, 1337-1340.
18. Joe, B.; Vijaykumar, M.; Lokesh, B.R. 2004. Crit. Rev. Food. Sci. Nutr. 44, 97-111.
19. Jurgens, T. M.; Frazier, E. G.; Schaeffer, J. M.; Jones, T. E.; Zink, D. L.; Borris, R. P. 1994. J. Nat. Prod. 57, 230-235.
20. Kikuzaki, H.; Kobayashi, M.; Nakatani, N. 1991. Phytochemistry 30, 3647-3651.
21. Kikuzaki, H.; Nakatani, N. 1993. J. Food Sci. 58, 1407-1410.
22. Kiuchi, F.; Goto, Y.; Sugimoto, N.; Akao, N.; Kondon, K.; Tsuda, Y. 1993. Chem. Pharm. Bull. 41, 1640-1643.
23. Kouno, I.; Kawano, N. 1985. Phytochemistry 24, 1845-1847.
24. Kress, W. J.; DeFilipps, R. A.; Farr, E.; Kyi, D. Y.Y. 2003. Smithsonian Institution Contributions from the United States Herbarium 45, 1-590.
25. Kress, W. J.; Prince, L. M.; Williams, K. J. 2002. Am. J. Bot. 89, 1682-1696.
26. Kuroyanagi, M.; Ueno, A.; Koyama, K.; Natori, S. 1990. Chem. Pharm. Bull. 38, 55-58.
27. Kuroyanagi, M.; Ueno, A.; Ujiie, K.; Sato, S. 1987. Chem. Pharm. Bull. 35, 53-59.
28. Lechtenberg, M.; Quandt, B.; Nahrstedt, A. 2004. Phytochem. Anal. 15, 152-158.
29. Lee, K. H. 2004. J. Nat. Prod. 67, 273-283.
30. Li, A.; Yue, G.; Li, Y.; Pan, X.; Yang, T. K. 2003. Tetrahedron Asymmetry 14, 75-78.

31. Majeed, M.; Badmeav, V.; Shivakumar, U.; Rajendran, R. 1995. Sabinsa Cooperation, NJ, USA.
32. Masuda, T.; Jitoe, A.; Isobe, J.; Nakatani, N.; Yonemori, S. 1993. Phytochemistry 32, 1557-1560.
33. Matsuda, H.; Morikawa, T.; Ninomiya, K.; Yoshikawa, M. 2001. Bioorg. Med. Chem. 9, 909-916.
34. Matsuda, H.; Morikawa, T.; Ninomiya, K.; Yoshikawa, M. 2001. Tetrahedron 57, 8443-8453.
35. Matsuda, H.; Morikawa, T.; Toguchida, I.; Ninomiya, K.; Yoshikawa, M. 2001. Chem. Pharm. Bull. 49, 1558-1566.
36. Matsuda, H.; Morikawa, T.; Toguchida, I.; Ninomiya, K.; Yoshikawa, M. 2001. Heterocycles 55, 841-846.
37. Matsuda, H.; Ninomiya, K.; Morikawa, T.; Yoshikawa, M. 1998. Bioorg. Med. Chem. Lett. 8, 339-344.
38. Matsuda, H.; Ninomiya, K.; Morikawa,T.; Yoshikawa, M. 1998. Bioorg. Med. Chem. Lett. 8, 339-344.
39. Newman, D. J. ; Cragg, G. M. 2007. J. Nat. Prod. 70, 461-477.
40. Newman, D. J.; Cragg, G. M.; Snader, K. M. 2000. Nat. Prod. Rep. 17, 215-234.
41. Ohshiro, M.; Kuroyanagi, M.; Ueno, A. 1990. Phytochemistry 29, 2201-2205.
42. Ohtsu, H.; Xiao, Z.; Ishida, J.; Nagai, M.; Wang, H. K.; Itokawa, H.; Su, C. Y.; Shih, C.; Lee, Y.; Tsai, M. Y.; Chang, C.; Lee, K. H. 2002. J. Med. Chem. 45, 5037-5042.
43. Petersen, O. G. 1889. Musaceae, Zingiberaceae, Cannaceae, Marantaceae. In A. Engler and K. Prantl [eds.], Die Natürlichen Pflanzenfamilien, 1st ed., 2, 1-43. Verlag von Wilhelm Engelmann, Leipzig, Germany.
44. Purseglove, J.W. 1974. Longman Group Ltd., London, UK.
45. Rajakrishnan, V.; Menon, V. P.; Rajashekaran, K. N. 1998. Phytotherapy Research, 12, 55-56.
46. Rasmussen, H. B.; Christense, S. B.; Kvist, L. P.; Karazmi, A. 2000. Planta Med. 66, 396-398.
47. Roth, G. N.; Chandra, A.; Nair, M. G. 1998. J. Nat. Prod. 61, 542-545.
48. Salvi, N.D.; George, L.; Eapen, S. 2000. Plant Cell. Tiss. Org. Cult. 62, 235-238.
49. Saralamp, P.; Chuakul, W.; Temsiririrkkul, R.; Clayton, T. 1996. Amatin, Bangok.
50. Sasaki, Y.; Fushimi, H.; Cao, S.Q.; Komatsu, K. 2002. Biol. Pharm. Bull. 25, 1593-1599.
51. Sasaki, Y.; Fushimi, H.; Komatsu, K. 2004. Biol. Pharm. Bull. 27, 144-146.
52. Shibuya, H.; Hamamoto, Y.; Cai, Y.; Kitagawa, I. 1987. Chem. Pharm. Bull. 35, 924-927.
53. Shiobara, Y.; Asakawa, Y.; Kodama, M.; Yasuda, K.; Takemoto, T. 1985. Phytochemistry 24, 2629-2633.
54. Shirgurkar, M.V.; John, C.K., Nadgauda, R.S. 2001. Plant Cell. Tiss. Org. Cult. 64, 5-11.
55. Simon, A.; Allais, D. P.; Duroux, J. L.; Basly, J. P.; Durand-Fontanier, S.; Delage, C. 1998. Cancer Lett. 129, 111-116.
56. Sirinivasan, K.R. 1953. J. Pharm. Pharmacol 5, 448-453.
57. Soudamini, K. K.; Unnikrishnan, M. C.; Soni, K. B.; Kuttan, R. 1992. J. Physiol. Pharmacol. 365, 239-243.
58. Suksamrarn, A.; Eiamong, S.; Piyachaturawat, P.; Byrne, L. T. 1997. Phytochemistry 45, 103-105.
59. Takano, I.; Yasuda, I.; Takeya, K.; Itokawa, H. 1995. Phytochemistry 40, 1197-1200.
60. Wessjohann, L.A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. 2005.Mol. Diversity 9, 171-186.
61. Yoshikawa, M.; Murakami, T.; Morikawa, T.; Matsuda, H. 1998. Chem. Pharm. Bull. 46, 1186-1188.