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GENERAL

TRUXILLIC AND TRUXINIC ACIDS–OCCURRENCE IN PLANT KINGDOM

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Abstract: For some years now there has been a systematic increase in the number of reports on new secondary metabolites of truxillic and truxinic acid derivatives. The paper offers a presentation of existing forms of cyclobutanodicarboxylic acids in plant kingdom, while considering their stereochemical structure and biosynthesis. Also presented are some results of research on the pharmacological activity of synthetic and natural derivatives of these compounds. The paper shows additionally the results of search in nature for compounds containing fragments of truxillic and truxinic acids seen against the occurrence of other compounds of cyclobutane derivatives in plant kingdom.

Keywords: truxillic and truxinic acids, cyclobutane, natural derivatives, biosynthesis, biological activity.

Phenolic compounds are a large and widely distributed group of chemical compounds in nature (1). They play a significant role in defending plants against pathogens (2–4) and possess numerous directions of interesting biological activity that seems important for humans in the light of their healing potential applications (5–7).

For the last six years now there has been a systematically growing number of reports on the occurrence in plants of new secondary metabolites, cyclodimeric derivatives of phenylpropenic acids – truxinic and truxillic acids (8–18).

Structure–wise, they can be seen as phenylpropane derivatives and indeed some authors find them accordingly as belonging to lignans (1, 17, 19).

Truxinic and truxillic acids are dimerization products of two cinnamic acid molecules and arise through making C–C bonds between the C–7,7' and C–8,8' carbons of these monomers (19).

Depending on the position of phenyl and carboxyl groups against the plane of created cyclobutane ring, truxinic acids comprise eight possible stereoisomers *cis/trans (E/Z)* with position of substituents phenyl–to–phenyl „head–to–head" (hh), while truxillic acids build up six possible stereoisomers *cis/trans (E/Z)* with positions of groups phenyl–to–carboxyl „head–to–tail" (ht) (the „head" as a phenyl substitutent, and the „tail" as a carboxyl group) (Figure 1) (20–26).

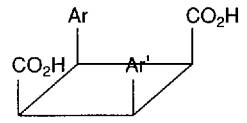
The presence of dimeric cinnamic acids in nature was initially revealed only in the structures of α– and β–truxillin – alkaloids *Erythroxylum coca* (Erythroxylaceae) (1,27,28). These compounds have, respectively a moiety of truxillic acid (α–truxillin) and truxinic acid (β–truxillin) (28). Truxillans as components of dimeric tropane alkaloids such as mooniines A and B (Figure 2) have been now discovered in other species of genus *Erythroxylum – Erythroxylum novogranatense* (28) and *Erythroxylum moonii* (13). Tropane alkaloids connected with one, two or three moieties of carboxylic acids have been also isolated from the species of genera Convolvulaceae and Solanaceae (13,27).

As discovered in the late 70s and the early 80s, some hydroxycinnamic acid derivatives, primarily p–coumaric acid (4–hydroxy–cinnamic) (P) and ferulic acid (4–hydroxy–3–methoxy–cinnamic) (F), mainly as isomers *trans* and their dimeric forms (cyclo– and dehydrodimers), are covalently bound to the cell–wall polysaccharides of graminaceous plants [20–26, 29–32] and a number of other species of families Angiospermeae (24).

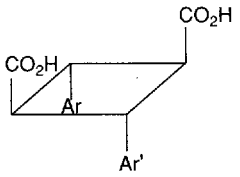
The moieties of acids in heteroxylan chains of cellular wall are estrified *via* their carboxyls to the hydroxyl group in position C(O)5 of α–L–arabinofuranose fragment that is bound by the hydroxyl group C(O)3 of β–D–xylopyranose (21, 24). This has been confirmed by Hartley et al (21), who isolated from wall hydrolisate of *Cynodon dactylon* (Poaceae) the following esterified trisaccharides: O–[5–O–((E)–p–coumaroyl)–α–L–arabinofuranosyl]–(1→3)–O–β–D–xylopyranosyl–(1→4)–D–xylopyranose and O–[5–O–(E)–p–feruloyl)–α–L–arabinofuranosyl]–(1→3)–O–β–D–xylopyranosyl–(1→4)–D–xylopyranose.

Dimeric forms of hydroxycinnamanates have been seen as of special biological importance since

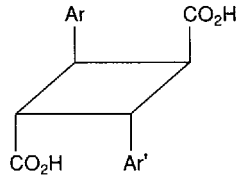
Dimerization „head-to-tail" (ht)



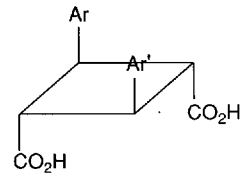
1 (cis-cis)



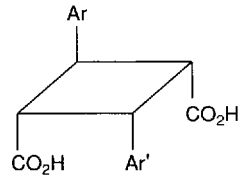
2 (trans-cis)



3 (trans-trans)



4 (trans-trans)



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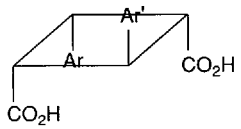
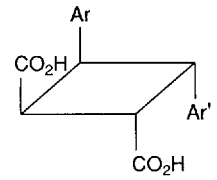
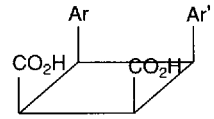


6 (cis-trans)

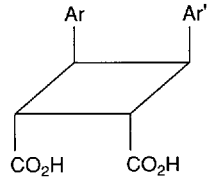
Dimerization „head-to-head" (hh)



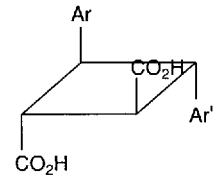
7 (cis-cis)



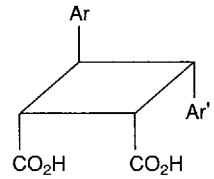
8 (cis-cis)



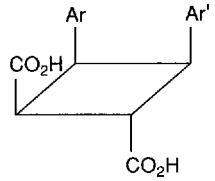
9 (trans-trans)



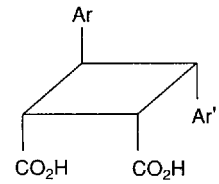
10 (trans-trans)



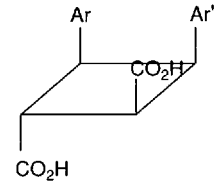
11 (trans-cis)



12 (cis-trans)

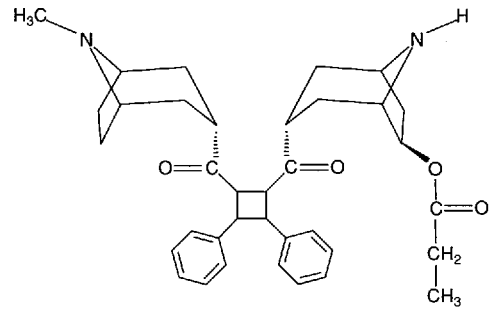


13 (trans-cis)

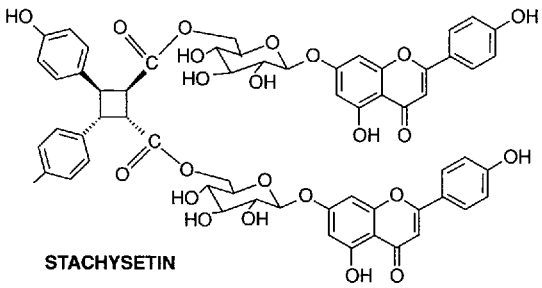


14 (trans-cis)

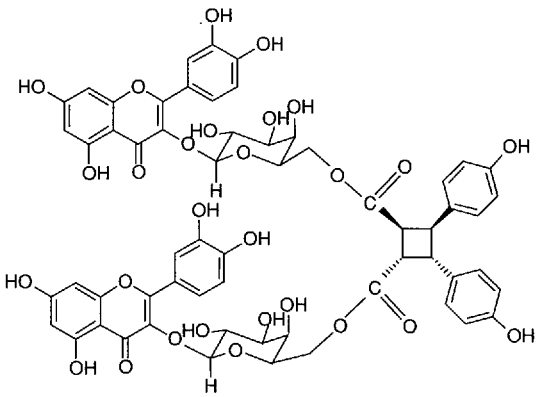
Figure 1. Stereodimers of p–coumaric acid (P) and ferulic acid (F): structures 1–5, 7–12, Ar=Ar'=4–hydroxyphenyl dimeric derivatives P, type PP; structures 1–5, 7–12, Ar=Ar'=4'–hydroxy–3–methoxyphenyl dimeric derivatives F, type FF; structures 1–14, Ar=4–hydroxyphenyl Ar'=4–hydroxy–3–methoxyphenyl dimeric derivatives P and F, type PF.



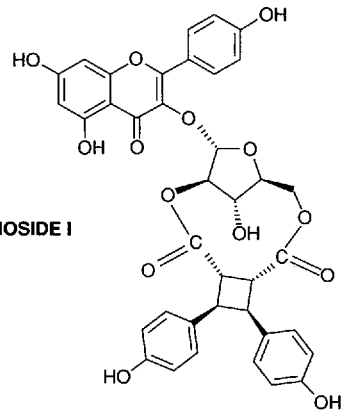
MOONIIN A



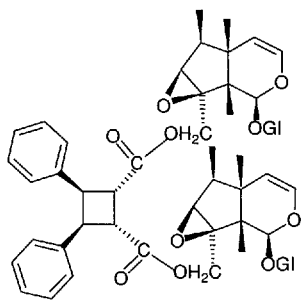
STACHYSETIN



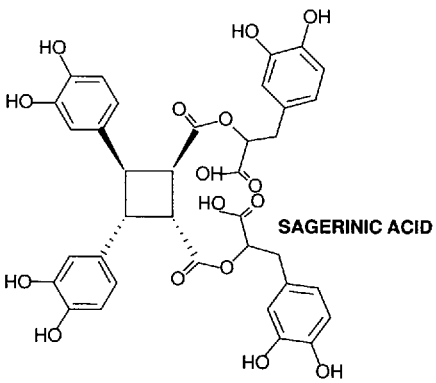
MONOCHAETIN



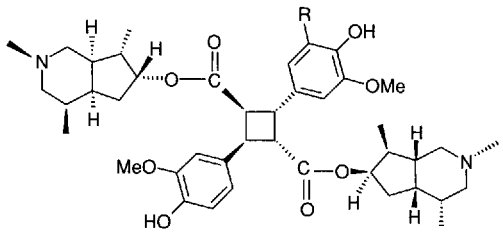
DAGLESIOSIDE I



TRUXINIC CATALPOL ESTER



SAGERINIC ACID



INCARVILATEINE R-H

METOXYINCARVILATEINE R-OMe

Figure 2. Structures of natural compounds derivatives of α–truxillic, β– and μ–truxinic acids.

they form „cross–linking" of polysaccharidic chains, and limit the digestibility of cell walls by ruminants likewise decrease of cell biodegradability (20, 22, 31). In the group of cellular wall dehydrodimers, 8–5', 8–8', 8–O–4' acids and 5–O–5' dicinnamic acids have been described so far (29, 30) whereas among cyclodimers in alkaline hydrolisates of *Cynodon dactylon* and *Lolium multijlorum* (Poaceae) 4,4'–dihydroxy–α–truxillic acid (type PP of stereodimer with a *trans/trans* configuration) (Figure 1), 4,4'–dihydroxy–3–methoxy–cc–truxillic acid (type PF of stereodimer with a *trans/trans* configuration) (Figure 1), and 4,4'–dihydroxy–3,3'–dimethoxy–α–truxillic acid (type FF of stereodimer with a *trans/trans* configuration) (Figure 1) (20, 21, 24) have been identified.

Eleven different PP stereodimers, eleven FF stercodimers and fourteen PF stereodimers, including substituted truxillic acids (ht) and substituted truxinic acids (hh) (Figure 1) can theoretically be formed *in vivo* from ferulic (F) and p–coumaric (P) acid monomers that are esterified in the chains of cellular wall heteroxylanes (20, 21). Creating a suitable stereodimer of the hh and ht type depends upon stereogeometry of the two initial monomers. If the moieties of phenolic acids to be joined are of *E* orientation, the resultant dimer has a *trans–trans* conformation, whereas for one moicty being isomer *E* and the other isomer *Z*, for example, the resultant dimer is of *trans/cis* type (20,22,23). Stereodimers found in nature mainly are of *trans/trans* form (20–22,24), however such as *cis/cis* dimers or of mixed *cis/trans* type (22) are also considered there, since free isomers Z originate in nature from the form *E* isomers when it is exposed to light, and the resultant *Z/E* mixtures are characterized by a slight dominance of isomer *E* (23).

Hartley et al. (20, 21, 24) have maintained that truxinic and truxillic acids originate in the process of photochemical dimerization in the cycle of plant growth and development. They have demonstrated that effectiveness of the daylight–induced conversion of the *E* form of p–coumaric acid to the 4,4'–dihydroxy–truxillic acid can reach even 100% (25, 26). Some influence of light upon the creation *in vivo* of cyclodimers in the cellular wall has been confirmed by other authors (22, 23, 25, 26, 31) who have also indicated that the necessary condition for photo–catalyzed cyclodimerization to be initiated is a maximum distance *ca* 4 Å between alkenyl groups of two parallel acid moieties.

Turner et al. (31) have ruled out the possibility of enzymatically mediated biosynthesis of cyclodimers by demonstrating that in wheat straw *Triticum aestivum* (Graminae) exposed to light the increase in dimeric forms was triple that for monomers, and that a similar increase was noticed in isomers *E* of basic phenolic acids *vis a vis* isomers *Z*.

Hanley et al. (22) suggest that cyclobutane diesters in the cellular wall may be formed in a process stimulated by free radicals, the mechanism of which is similar to that of building up lignin or the 5–0–5'–dehydrodimers of ferulic acid (29, 30). Experiments carried out with the use of enzymes from peroxidases group have indicated, however there are no free radical reactions in biosynthesis of these compounds (21).

First reports on the occurrence of dimeric phenolic acids outside the cellular wall in either free form or as ester–bound moieties began to appear in the early 90s. They covered mainly derivatives of α–truxillic acid (type PP of stereodimer ht with a configuration of *trans/trans* – compound 3, Figure 1), p–truxinic acid (type PP of stereodimer hh with a configuration of *trans/trans* – compound 9, Figure 1), and α–truxinic acid (type PP of stereodimer hh in a configuration of *cis/cis* –compound 7, Figure 1) (8, 9, 16).

Urones et al. (8) have identified in the aerial parts of *Halimium verticillatum* (Cistaceae) a free α–truxillic acid in the form of methyl ester obtained through methylation with diazomethane of the acid fraction of the ethyl acetate extract.

Dimberg et al. (16) have informed the isolation from oat grains *Avena sativa* (Gramineae) of truxinic acid glycoside found outside the cellular wall, namely 4,4'–dihydroxy–3,3'–dimethoxy–β–traxinic saccharose diester that had ester linkages in positions C–3" and C–6" of fructose. Similar saccharose derivatives with other phenolic acids, for example with ferulic acid, had been discovered earlier, and they are now widely reported in the literature (33).

As the first phytochemical compound, a secondary metabolite with a truxinic acid moiety in its structure was described –apart from alkaloids of the *Erythroxylum* genus (1, 27, 28) in 1995 a flavonoid – stachysetin – di–7–O–(6"–trans,6"–cis–p,p'–dihydroxy–μ–truxinoyl))–β–D–glucoside apigenin (Figure 2) (9). Stachysetin is commonly found in the herb *Stachys aegyptiaca* (Labiatae) along with other compounds there that are acylated flavonoids and comprise apigenin 7–O–(6"–β–coumaroyl)–(3–D–glucoside and naringenin 7–O–(6"–p–coumaroyl)–β–D–glucoside. Until 2001 this compound had been seen as a unique flavonoid compound formed by esterification of two carboxyl groups of μ–truxinic acid with two alcohol sugar groups that originated from two moieties of flavone – apigenin 7–O– glucoside (9, 17).

El–Ansari et al. (9) suspected initially that stachysetin was an artefact, that arose under the influence of daylight in the course of plant material extraction from two molecules of apigenin 7–O–(p–coumaroyl)–β–D–glucoside, yet their hypothesis was not confirmed by chromatographic control of methanolic extracts that were prepared with no access of light.

Diglucosylflavonoid esters of dicarboxilic acids are in actual fact very rarely encountered in plants. Itokawa et al. (34) have isolated malonyldiglucosylflavone – agastachin from *Agastache rugosa* (Labiatae) and presented its probable structure. Horie et al. (35) separated from *Citrus sudachi* (Rutaceae) sudachinin, the compound in which sudachin (5,7,4'–trihydroxy –6,8,3'–trimethoxyflavone) 4'–O– and 7–O–glucosides are substituted in positions C–6" of their glucose moieties by fragment of 3–hydroxy–3–methylglutaric acid.

The second lignan diester of flavonoid diglycoside to be isolated was a derivative of flavonol – quercetin (3), obtained from the leaves of *Monochaetum multiflorum* (Melastomataceae). Monochaetin – di–3–O–(6"–*trans*, 6"–cis–p,p'–dihydroxy–μ–truxinoyl)–β–D–galactoside quercetin (Figure 2) originates in the plant – according to Isaza et al. (3) as a result of photochemical addition of two molecules of quercetin 3–O–(6'–caffeoyl)–β–D–galactoside. In the plant material, apart from the above compounds, occur also other phenolic esters that include quercetin 3–O–(6'–caffeoyl)–β–D–glucoside, 4–O–(6'–galloyl)–β–D–glucopyranosyl)–*cis*–p–coumaric acid, 6'–O–galloylprunasin, and benzyl 6'–O–galloyl–β–D–glucopyranoside (3).

From the needles of green Douglas fir – *Pseudotsuga menziesii* (Pinaceae) the first flavonoid truxinoylmonoglucoside was isolated and that was kaempferol 3–O–arabinofuranoside esterified with acid in positions C–5" and C–2" of sugar moiety (Figure 2) (17). The compound is accompanied in the plant by its non–dimerized counterpart–kaempferol 3–O–[2",5"di(E)–coumaroyl]–arabinofuranoside, a flavonoid of previously unknown structure in nature, and a set of three mono– and diesters of kaempferol 3–O–glucoside (17).

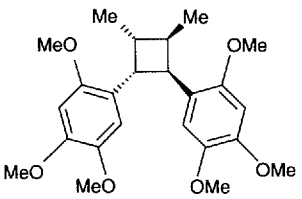
The list of other compounds of truxinic acid found so far in plant kingdom should also include iridoid – 4,4'–dimethoxy–β–truxinic acid catalpol diester (Figure 2) from *Premma subscandens* (Verbenaceae) (15), and sagerinic acid – 3,4–dihydroxyphenylpropan–8–ol μ–truxinic diester (Figure) from *Salvia officinalis* (Labiateae) (14). The latter is probably a product of photochemical cyclization of rosmarinic acid (14), while items on the above list represent truxinic acid amide –caracasandiamide from *Verbesina caracasana* (Asteraceae) (16) as well as such alkaloids as incarvillateine and methoxyincarvilateine, an N–iridoid truxillic acid diesters (Figure 2) from *Incarvillea sinensis* (Bignoniaceae) (25, 26).

No discussion on cyclobutanodicarboxylic acids should miss the fact that in nature there are other compounds with a cyclobutane ring in their structure. They are no doubt a rarity there, and the reports on them focused on a group of phenylpropane derivatives – neolignans with a symmetrically substituted cyclobutane: andamanicin, magnosalin from *Magnolia salicifolia* (Magnoliaceae) (37) (Figure 3) as well as *Piper sumatranum* (Piperaceae) (38), heterotropan from *Heterotropa takaoi* (Aristolochiaceae) (39) (Figure 3), pellucidin A from *Peperomia pellucida* (Piperaceae) (40) (Figure 3), pachypophyllin–*bisnor* lignan from *Pachypodanthium staudtii* (Annonaceae) (41), and lignans of the asymmetric configuration of substitutents in the cyclobutane ring from *Mosla scabra* (Lamiaceae) – moslolignans A and B (42) (Figure 3). As in the above compounds, a symmetrical structure is also present in dimeric chalcone from *Goniothalamus thwaitesii* (Annonaceae) with a cyclobutane system that is substituted by phenyl groups in positions 3β, 4α and by benzoyl substituents in positions 1β, 2α (43) (Figure 3), cycloanchinopeptolide C – a dimeric peptide alkaloid coming from Mediterranean sponge *Anchinoe tenatior* (Anchinoideae) (44) as well as piplartine–dimeric piperidine alkaloid isolated from the species of genus *Piper* (Piperaceae) (45–47). Stereochemical structure of some of these compounds still remains unclear (41, 44–47). A number of dimeric phenylbutanoids and other phenylcyclobutane derivatives have been isolated from the rhizomes and leaves of *Alpinia flabellata* (Zingiberaceae) (48) (Figure 3).

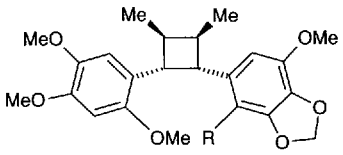
Cyclization products of methyl esters of cinnamic and p–coumaric acids with a cyclobutane ring formation, namely gratissimin from *Ocimum gratissimum* (Lamiaceae) (49), and α–diplicatin B (Figure 3) from *Psoraleaplicata* (Leguminoseae) (50) are believed to include.

An interesting group of flavonoids are homoisoflavanons – scillascillins (Figure 3) and this is for the presence of a fourth spirocyclic butenyl ring in them. They are isolated from species *of Eucomis humilis* and *Drimiopsis maculata* from family Hyacinthaceae that has been become separated from Liliaceae and is richly represented in the flora of South Africa (51).

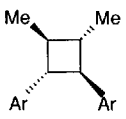
Biological activity of natural compounds containing either truxinic or truxillic acids has been



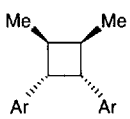
ANDAMANICIN



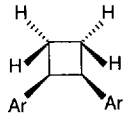
MOSLOLIGNAN A **R-H**
MOSLOLIGNAN B **R-OMe**



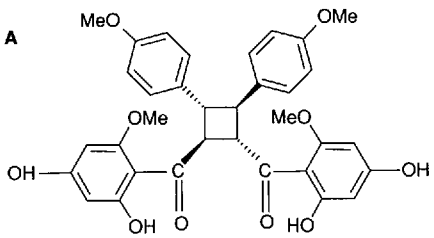
MAGNOSALIN



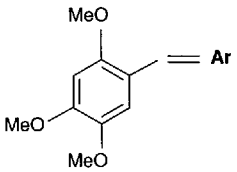
HETEROTROPAN

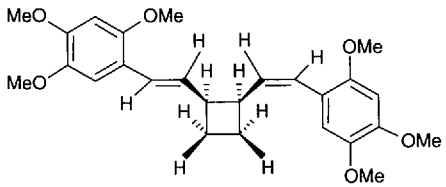


PELLUCIDIN A

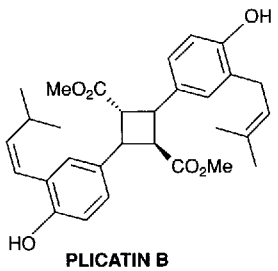


DIMERIC CHALCONE FROM *GONIOTHALAMUS THWAITTESII*

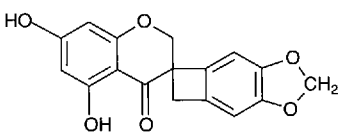




PHENYLBUTANOID FROM *APINIA FLABELLATA*



PLICATIN B



SCILLASCILLIN 1

Figure 3. Structures of compounds– derivatives of cyclobutane isolated from plant kingdom.

investigated only to a very small degree. It was only Atta –ur–Rahman et al. (13) who demonstrated the lack of antibacterial activity of alkaloids from *Erythroxylum moonii,* in opposite to strong antifungal properties thereof, which were then confirmed in tests against 10 species of fungi. Some other investigations have shown a hypotensive activity of caracasandiamide (10). Compared with these data, the results from pharmacological experiments on synthetic derivatives of α–truxillic acid seem truly encouraging (52–56). Antagonists of nicotine receptors, quarternary ammonium salts of esters of α–truxillic acid–anatruxonium and cyclobutonium have been clinically used as neuromuscular blockers, the so called myorelaxants (52–53). Nowadays, a number of bis–N–quarternary and tertiary esters of α–truxillic acid are seen as very promising agents in the group of potential inhibitors of rinic receptors especially of M_2 mAChR subtype (54–56).

REFERENCES

1. Bruneton J. Pharmacognosy, Intercept, New York, 1999.
2. Bergvinson D.J., Arnason J.T., Hamilton R.I., Tachibana S., Towers G.H.N.: Environ. Entomol. 23, 1516 (1994).
3. Grayer R.J., Harborne J. B.: Phytochemistry 37, 19 (1994).
4. Faulds C.B., Williamson G.: J. Sci. Food Agric. 79, 393 (1999).
5. Kroes B.H., Berg A.J.J., Ufford H.C.Q., Dijk H., Labadie R.P.: Planta Med. 58, 499 (1992).
6. Hirabayashi T., Ochiai H., Sakai S., Nakajima K., Terasawa K.: Planta Med. 61, 221 (1995).
7. Bergman M., Varshavsky L., Gottlieb H.G., Grossman S.: Phytochemistry 58, 143, (2001).
8. Urones J.G., Marcos I.S., Diez Martin D., Rodilla J.M.L., Dinis de Mendoca D. I. M., Williams D.J.: Phytochemistry 36, 529 (1994).
9. El–Ansari M.A., Nawwar M. A., Saleh N.A.M.: Phytochemistry 40, 1543 (1995).
10. Monache G.D., Botta B., Monache F.D., Espinal R., DeBonnevaux S., DeLuca C., Botta M., Corelli F., Dei D., Gacs–Baitz E., Carmignani M.: Bioorg. Med. Chem. Lett. 6, 233 (1996).
11. Chi Y.–M., Hashimoto F., Yan W.–M., Nohara T.: Phytochemistry 46, 763 (1997).
12. Chi Y.–M., Yan W.–M., Li J.–S.: Phytochemistry 29, 2376 (1990).
13. Atta –ur–Rahman K.F., Nighat F., Shabbir M., Hemalal K.D., Tillerkerante L.M.: Phytochemistry 48, 377 (1998).
14. Lu Y., Foo L.Y.: Phytochemistry 51, 91 (1999).
15. Sudo H., Ide T., Otsuka H., Hirata E., Takushi A., Shinzato T., Takeda Y.: Chem. Pharm. Bull. 48, 6542 (2000).
16. Dimberg L.H., Andersson R. E., Gohil S., Bryngelsson S., Lungren L. N.: Phytochemistry 56, 843 (2001).
17. Isaza J.H., Ito H., Yoshida T.: Phytochemistry 58, 321 (2001).
18. Krauze–Baranowska M., Sowiński P., „Flavonoids from *Pseudotsuga menziesii*" Book of Abstracts ‚JLead compound from higher plants" P028 International Symposium of PSE, Laussanne, Switzerland 11–14.09.2001.
19. Lewis N.G., Davin L.B. in Comprehensive Natural Products Chemistry, (Ed. Sankawa U.), vol. 1, p. 647, Elsevier, Amsterdam 1999.
20. Hartley R.D., Morrison III W.H., Towers G.H.N.: Phytochemistry 29, 3699 (1990).
21. Hartley R.D., Morrison III W.H., Himmelsbach D.S., Borneman W.S.: Phytochemistry 29, 3705 (1990).
22. Hanley A. B., Russell W.R., Chesson A.: Phytochemistry 33, 957 (1993).
23. Morrison III W.H., Hartley R.D., Himmelsbach D.S.J.: J. Agric. Food Chem. 40, 768 (1992).
24. Hartley R.D., Whatley F.R., Harris P.J.: Phytochemistry 27, 349 (1988).
25. Ford C.W., Hartley R.D.: J. Sci. Food Agric. 46, 301 (1989).
26. Ford C.W., Hartley R.D.: J. Sci. Food Agric. 50, 29 (1990).
27. Lounasmaa M., Tamminen T. in The Alkaloids, (Ed.Cordell G. A.), vol. 44, p. 1, Academic Press, San Diego, 1993.
28. Novak M., Salemink C., Khan I.: J. Ethnopharmacology 10, 267 (1984).
29. Ralph J., Quideau S., Grabber J.H., Hatfield R.D.J.: Chem. Soc. Perkin Trans I, 3485 (1994).
30. Saulnier L., Crepeau M.–J., Lahaye M., Thibault J.F., Garcia–Conesa M.T., Kroon P.A., Williamson G.: Carbohydr. Res. 320, 82 (1999).
31. Turner L.B, Mueller–Harvey I., McAllan A.B.: Phytochemistry 33, 791 (1993).
32. Tachibana S., Onkubo K., Towers G.H.N.: Phytochemistry 31, 81 (1992).
33. Harrison L.J., Sia G–L., Sim K.–Y., Tan T.–W., Connoly J.D., Lavaud C., Massiot G.: Phytochemistry 38, 1497 (1995).
34. Itokawa H., Sato H., Takeya K.: Chem. Pharm. Bull. 29, 1777 (1981).

35. Horie T., Tsukayama M., Yamada T., Miura L, Nakayama M.: Phytochemistry 25, 2621 (1986).
36. Harborne J.B., Baxter H. The Handbook of Natural Flavonoids, Wiley, Chichester 1999.
37. Kikuchi T., Kadota S., Yanada K., Tanaka K., Watanabe K., Yoshizaki M., Yokoi T., Shingu T.: Chem. Pharm. Bull. 31, 1112 (1983).
38. Malhotra S., Koul S.K., Taneja S.C., Pushpangalan P., Dhar K.L. Phytochemistry 25, 2733 (1990).
39. Yamamura S., Niwa M., Nonoyama M., Terada Y.: Tetrahedron Lett. 49, 4891 (1978).
40. Bayma J. de C., Arrauda M.S.P., Mueller A.H., Arrauda A.C., Canto W.C.: Phytochemistry 55, 779 (2000). 41.Ngadjui B. T., Lontsi D., Ayafor J.F., Sondengam B.L.: Phytochemistry 28, 231 (1989).
42. Wang Q., Terraux C., Marston A., Tan R–X., Hostettmann K.: Phytochemistry 54, 909 (2000).
43. Sedel V., Francois B., Waterman P.O.: Phytochemistry 55, 439 (2000).
44. Casapullo A., Minale L., Zollo F.: J. Nat. Prod. 57, 1227 (1994).
45. Filho R.B., De Souza M.P., Mattos M.E.O.: Phytochemistry 20, 345 (1981).
46. Duh C.–Y., Wu Y.–C., Wang S.–K.: J. Nat. Prod. 53, 1575 (1990).
47. Maxwell A., Rampesad D.: J. Nat. Prod. 54, 1150 (1991).
48. Kikuzaki H., Tesaki S., Yonemori S., Nakatani N.: Phytochemistry 56, 109 (2001).
49. Vilian C., Hubert A., Dupont L., Markham K.R., Wollenweber E.: Z. Naturforsch. 42c, 1135(1987).
50. Hamed A.I., Springuel L., El–Emary N.A., Mitome H., Yamada Y.: Phytochemistry 36, 1257 (1997).
51. Koorbanally Ch., Mulholland D.A., Crouch N. „Scillascillins from the southern afiican Hyacinthaceae" Book of Abstracts „Lead compound from higher plants" P006, International Symposium of PSE, Laussanne, Switzerland 11–14.09.2001.
52. Kharkevich D.A., Fisenko V. P.: Arch. Int. Pharmacodyn. Ther. 251, 255 (1981).
53. Kharkevich D.A.: Ann. Inst. Super. Sanita. 20, 21 (1984).
54. Kharkevich D.A., Skoldinov A.P., Samailov D.N., Shorr V.A.: Farmakol. Toksikol. 43, 645 (1980).
55. Lysikowa M., Fuksowa K., Elbert T., Jakubik J., Tucek S.: Br. J. Pharmacol. 127, 1240 (1999).
56. Ubransky M., Proska J., Ricny J., Drasar P.: Collection 64, 1980 (1999).

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