Review

Ethnobotany, phytochemistry and pharmacology of *Podocarpus sensu latissimo* (s.l.)

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Abstract

The genus *Podocarpus sensu latissimo* (s.l.) was initially subdivided into eight sections. However, based on new information from different morphological and anatomical studies, these sections were recognised as new genera. This change in nomenclature sometimes is problematic when consulting ethnobotanical data especially when selecting plants for pharmacological screening, thus there is a need to clear any ambiguity with the nomenclature. Species of *Podocarpus* s.l. are important timber trees in their native areas. They have been used by many communities in traditional medicine and as a source of income. *Podocarpus* s.l. is used in the treatment of fevers, asthma, coughs, cholera, distemper, chest complaints and venereal diseases. Other uses include timber, food, wax, tannin and as ornamental trees. Although extensive research has been carried out on species of *Podocarpus* s.l over the last decade, relatively little is known about the African species compared to those of New Zealand, Australia, China and Japan. Phytochemical studies have led to the isolation and elucidation of various terpenoids and nor- and bis-norditerpenoid dilactones. Biflavonoids of the amentoflavone and hinokiflavone types have also been isolated. Nor- and bis-norditerpenes are said to be taxonomic markers for this genus. Recent *in vitro* and *in vivo* studies have shown antitumor, antimicrobial, anti-inflammatory, antioxidant, larvicidal, plant and insect growth regulation activities. Various studies have yielded important natural bioactive products and two of them are worth mentioning. Taxol, a significant anticancer agent has been isolated from *Podocarpus gracilior* and totarol, a diterpenoid isolated from various species and now commercially produced as a potent antibacterial and antioxidant agent. Findings from this review supports the use of an ethnobotanical and chemotaxonomical approach in selecting plants for pharmacological screening since most of the species in the different morphological groups have similar uses. Also the isolated compounds have chemotaxonomic value amongst the groups. Some of the biological activities identified from extracts and compounds isolated from *Podocarpus* s.l. support the rationale behind the medicinal uses of these species.

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**Keywords:** Chemotaxonomy; Ethnobotany; Pharmacology; *Podocarpus*; Traditional uses

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1. Introduction

1.1. Morphology

Until the 1970s, the Podocarpaceae family was composed of seven genera; *Podocarpus* L’ Her. ex Pers., *Dacrydium* Sol. ex Forst., *Phyllocladus* Rich. Ex Mirb., *Acmopyle* Pilg., *Microcachrys* Hook.f., *Saxegothaea* Lindl. and *Pherosphaera* W. Archer bis (= *Microstrobos* J. Garden & L.A.S. Johnson, nom. inval.: Brummitt et al., 2004). Based on the leaf anatomy, *Podocarpus* was initially subdivided into eight sections; *Afrocarpus* J. Buchholz & N. E. Gray, *Dacrycarpus* Endl., *Eupodocarpus* Endl., *Microcarpus* Pilg., *Nageia* (Gaertn.) Endl., *Polypodiopsis* C. E. Bertrand, *Stachycarpus* Endl., and *Sundacarpus* J. Buchholz & N. E. Gray (Buchholz and Gray, 1948). The African taxa were placed in *Podocarpus* (Leistner, 1966). In the past 25 years, research, based on new information from studies of wood anatomy, embryology and chemistry, have proposed new genera and endorsed recognition of the 19th century segregates from *Podocarpus sensu latisimo* (s.l.) and *Dacrydium* (s.l.) (De Laubenfels, 1969, 1972, 1985; Quinn, 1982; Page, 1989). However, herbaria and authors of floristic works have been slow to accept these changes, probably because the broadly defined genera are unnatural.

1.2. Taxonomy

Subsequent studies based on morphological and molecular (DNA sequence) data showed that *Podocarpus* section *Afrocarpus* is related to *Podocarpus* section *Nageia*, and the other sections were regarded as paraphyletic (Kelch, 1997). More recent studies by Conran et al. (2000) and Sinclair et al. (2002), concludes that there is considerable molecular evidence favouring the generic level recognition of *Afrocarpus* and the other genera as proposed by Page (1989). Thus Podocarpaceae is now represented by two genera in Africa: *Podocarpus* and *Afrocarpus*, and the species *Podocarpus falcatus* (Thunb.) R. Br. ex Mirb. and *Podocarpus gracilior* Pilg. are now *Afrocarpus falcatus* (Thunb.) C. N. Page and *Afrocarpus gracilior* (Pilg.) C. N. Page (Barkera et al., 2004). Cladistic analysis of morphological, anatomical and embryological characteristics indicated strongly the segregation of the new genera and the relationships between closely related genera. For instance, the morphological analysis of Podocarpaceae using the single most parsimonious tree based on 54 characters showed the genera *Nageia*, *Retrophyllum* and *Afrocarpus* which initially were included in *Podocarpus* s.l. to belong to the tropical clade and very closely related. *Dacrycarpus* s.l., though a tropical clade, was separated from *Podocarpus* s.l. because of being a tetragonal-leaved clade (Kelch, 1997). A recent analysis of the family based on rbcL sequences retrieved three main clades (Podocarpaceae, Dacrydoid and Prumnopityoid) and *Afrocarpus*, *Nageia* and *Retrophyllum* were grouped just as Kelch’s analysis indicated (Conran et al., 2000). This study also placed *Sundacarpus amarus* within *Prumnopitys*, suggesting it is just a specialised member of that genus and is not itself a good genus (Quinn and Price, 2003).

1.3. Distribution

In the early 1940s and 1950s, the biogeographical information on Podocarpaceae was published (Florin, 1940; Buchholz and Gray, 1948; Li, 1953). However, due to great changes in the taxonomy of Podocarpaceae (De Laubenfels, 1969; Quinn, 1982; Molloy, 1995; Kelch, 1997, 1998), the earlier biogeographical statement is rendered invalid. For example the genus *Dacrydium* is not present in both western and eastern hemispheres (Sinclair et al., 2002). The conventional view was that the Podocarpaceae had a Gondwanan origin and migrated northwards to reach the present northerly limits in the Caribbean, Ethiopia and eastern Asia. The only limitation to this view is that it does not consider the numerous Laurasian fossils that have been assigned to Podocarpaceae (Mill, 2003). The greatest generic diversity of Podocarpaceae is in Malesia and Australasia where 17 of the 19 living genera are found. Malesia, New Caledonia and New Zealand each have eight genera, seven genera in Australia, four genera in South America and Africa, and Asia two genera each. With respect to living endemism, Australia has three endemic genera (*Lagarostrobos*, *Microcachrys* and *Pherosphaera*), two for New Zealand (*Halocarpus* and *Manoao*), New Caledonia, South America and Africa each have one (*Parasitaxus*, *Saxegothaea* and *Afrocarpus*, respectively) (Mill, 2003).

1.4. Chemistry

Presence or absence of different compounds can be used to relate the new and the old taxa. For example, flavonoids can be
a useful chemotaxonomic tool in this group of plants, since biflavonoids of the amentoflavone and hinokiflavone groups have been shown to be good taxonomic markers in the great majority of Podocarpus s.l. (Roy et al., 1987). In the recognition of the new segregated genera of Podocarpus s.l., presence or absence of different monomer flavonoid glycosides seemed important. Thus, Dacrycarpus is demarcated by the presence of 3-methoxyflavones, while Prumnopitys and Podocarpus are characterized by the predominance of flavonol 3-O-glycosides and flavone C-glycosides, respectively (Markham et al., 1985). Since nor- and bis-norditerpenes are taxonomic markers of these species, the possibilities that the related taxa will have similar biological activities or bioactive compounds cannot be overruled.

The nomenclature used in earlier literature on the uses of Podocarpus s.l. species does not match the current taxonomical nomenclature. Change of names and frequently incorrect citation is quite a problem for all ethnobotanical data, and thus care needs to be taken when consulting the original literature to unambiguously confirm that a plant selected for a particular study is in fact the same species cited (Lourens et al., 2008). This paper attempts to summarize the current state of knowledge about the genus Podocarpus s.l. and the revised segregated genera with a focus on ethnobotany, phytochemistry and pharmacology. These findings in relation to the African Podocarpaceae will be evaluated as a key to ethnomedical logical studies. This will provide researchers with a concise source of information on Podocarpus s.l., especially those who are interested on a local scale. The occurrence of similar compounds between Podocarpus s.l. and the revised genera supports a phylogenetic affinity and hence it might be useful to assay for these pharmacological activities and bioactive compounds in other members of Podocarpaceae. Thus in addition to ethnomedical approaches of selecting plants for screening, chemotaxonomic relationships between different species and pharmacological activities may also be employed. This study will also try to clear any ambiguity in terms of correct taxonomical naming in relation to traditional uses.

2. Ethnobotanical uses of Podocarpus

In order to clarify the taxonomical/nomenclatural ambiguity surrounding the genus Podocarpus s.l., Table 1 provides information on the new names and the synonyms according to the current classifications while Tables 2 and 3 indicate the ethnobotanical uses of Podocarpus s.l. as cited by various literatures and for this purpose the taxa used by the authors have been maintained.

2.1. Non-medicinal uses

Podocarpus species are important timber trees in their native areas (Table 2) (Hora, 1981). The timber is fine-grained, non-resinous, light and moderately strong. This, combined with its aesthetic appearance and weight advantage over pine, makes it a potentially superior substitute wood for use as beams, rafters, flooring, ceilings, doors, planks and furniture (Palmer and Pitman, 1972). For example, fine timber known as Yellowwood is obtained from the South African species P. falcatus (Thunb.) R. Br. ex Mirb. and Podocarpus latifolius (Thunb.) R. Br. ex Mirb., whereas the ‘Totara’ is obtained from the New Zealand species Podocarpus totara G. Benn. Ex D. Don (Hora, 1981). The timber from most species of Podocarpus and related genera is used for furniture making, boat building, interior works and house construction (Table 2).

Species of Podocarpus s.l. such as Podocarpus elongatus, (Aiton) L’Hér. ex Pers. P. falcatus, Podocarpus henkelii Stapf ex Dallim. & A. B. Jacks. P. latifolius, Podocarpus neriifolius D. Don., Podocarpus nubigenus Lindl., Podocarpus salignus D. Don. and P. totara are used as ornamental trees, mostly for landscaping (Table 2). The fruits of Podocarpus dacyryoides A. Rich., P. neriifolius, Podocarpus nivalis Hook., P. salignus, P. totara are eaten raw or cooked, while edible fruits of Podocarpus nagi (Thunb.) Zoll. & Mortiz are sold in the local markets in the Himalayas (Table 2). In Queensland, the fruits of Podocarpus spinulosa R. Br. are used locally for jams and preserves (Uphof, 1968; Usher, 1974). The young leaves of P. nagi are occasionally parboiled and eaten, while Podocarpus elatus R. Br. ex Endliener is a wild harvested Australian indigenous food. The fleshy stem is eaten by the Aborigine people and the fruits eaten raw or cooked (Cribb and Cribb, 1981). Other products obtained from this genus include dyes, tannins and waxes (Table 2).

In South Africa systematic timber harvesting of P. falcatus and P. latifolius is permitted by the Department of Water Affairs and Forestry to supply the small-scale furniture workshops and local timber industries. On average 750 m³ round logs are harvested annually and although this is relatively small the industry makes substantial contribution to the local economy creating over 500 jobs and is worth R16 million annually (Van der Merwe, 1998). Some species of Podocarpus are used for cultural purposes in South Africa. For example the bark of P. henkelii is used as a love charm by the Zulu. It is chewed and spat out into the wind, as the name of the loved one is repeated, while the bark of P. falcatus is burned in the kraal as a charm to prevent the cattle from straying (Hutchings et al., 1996).

2.2. Medicinal uses

Table 3 summarizes the medicinal uses of several species of Podocarpus s.l. which are utilized in treating all manner of ailments in various parts of the world. The bark of P. nagi (Thunb.) Zoll. & Mortiz is used traditionally in Ayurvedic medicine as an antiseptic, astringent and carminative and has proved to be useful in the treatment of fevers, asthma and coughs (Chopra et al., 1986). Mixed with ginger, it is used as a rubefacient in the treatment of cholera (Duke and Ayensu, 1985). In China the stem bark is used as a wash in the treatment of arsenic poisoning, skin diseases and ulcers. The fruit is carminative, pectoral and stomachic. The seed is used in the treatment of cholera, heart ailments, stomach diseases and for sweaty feet (Duke and Ayensu, 1985).

P. totara used in Māori medicines dates back at least 100 years. The smoke from shavings of totara is used to treat
### Table 1
Current scientific names, synonyms and geographical distribution of species of *Podocarpus sensu lato* and the segregated genera.

| Species name | Synonym | Geographical distribution | References |
|--------------|---------|---------------------------|------------|
| *Afrocarpus falcatus* (Thunb.) C. N. Page | *Podocarpus falcatus* (Thunb.) R. Br. ex Mirb.; *Afrocarpus gaussenii* (Woltz) C.N. Page; *Decussocarpus falcatus* (Thunb.) de Laub.; *Nageia falcata* (Thunb.) Kunztee; *Nageia falcata* var. *gaussenii* (Woltz) Silba; *Podocarpus gaussenii* Woltz; *Podocarpus gracilimus* Stapf; *Podocarpus meyerianus* Endl.; *Taxus falcata* Thunb. | Southern Africa and East Africa | (Leistner et al., 1995; Bisby et al., 2008) |
| *Afrocarpus gracilior* (Pilg.) C. N. Page | *Podocarpus gracilior* Pilg.; *Decussocarpus gracilior* (Pilg.) De Laub.; *Decussocarpus gracilior* (Pilg.) Laubenf.; *Nageia falcata* (Thunb.) Carr. var. *gracilior* (Pilg.) Silba; *Nageia falcata* var. *gracilior* (Pilg.) Silba | Ethiopia, Kenya, Tanzania, Uganda | (Farjon, 1998; GRIN, 2009) |
| *Afrocarpus mannii* (Hook. f.) C. N. Page | *Decussocarpus mannii* (Hook.f.) de Laub.; *Podocarpus mannii* Hook. f. | West Central Tropical Africa: Sao Tome and Principe | (Farjon, 1998; GRIN, 2009) |
| *Afrocarpus usambarensis* (Pilg.) C. N. Page | *Decussocarpus falcatus* (Thunb.) de Laub.; *Decussocarpus gracilior* (Pilg.) Laubenf.; *Nageia falcata* (Thunb.) Carr. var. *gaussenii* (Woltz) Silba; *Podocarpus falcatus* (Thunb.) Endl.; *Podocarpus gaussenii* Woltz; *Podocarpus gracilimus* Stapf; *Podocarpus meyerianus* Endl.; *Taxus falcata* Thunb. | Ethiopia, Kenya, Tanzania, Uganda | (Farjon, 1998; GRIN, 2009) |
| *Amentotaxus argotaenia* (Hance) Pilg. | *Cephalotaxus argotaenia* (Hance) Pilg.; *Nageia argotaenia* (Hance) Kuntze; *Podocarpus argotaenia* (Hance) Kuntze | China, Hong Kong, Taiwan, Vietnam | (Farjon, 2001; Vie et al., 2006; Germplasm Resources Information Network, GRIN, 2009) |
| *Dacrycarpus compactus* (Wasscher) de Laub. | *Bracteocarpus compactus* (Wasscher) A.V. Bobrov & Melikyan; *Podocarpus compactus* Wasscher | Papua New Guinea | Bisby et al. (2009) |
| *Dacrycarpus dacydioides* (A. Rich.) de Laub. | *Dacrydium excelsum* D. Don; *Nageia dacydiodes* (A.Rich.) F. Muell.; *Nageia excels* (D. Don) Kunztee; *Podocarpus dacydioides* A. Rich.; *Podocarpus excelsus* (D. Don) Druce; *Podocarpus thujoides* R. Br. ex G. Benn. | New Zealand | (Bisby et al., 2009; Germplasm Resources Information Network, GRIN, 2009) |
| *Dacrycarpus imbricatus* (Blume) de Laub. | *Dacrycarpus imbricatus* var. *curvulus* (Miq.) de Laub.; *Dacrycarpus imbricatus* var. *imbricatus* (Blume) de Laub.; *Dacrycarpus imbricatus* var. *palatus* de Laub.; *Podocarpus cupressinus* R. Br. ex Mirb., *Podocarpus imbricatus* Blume | China, Fiji, Malaya, Papua New Guinea, Philippines, Sumatra | (Bisby et al., 2009; Germplasm Resources Information Network, GRIN, 2009) |
| *Nageia fleuryi* (Hickel) de Laub. | *Decussocarpus fleuryi* (Hickel) de Laub.; *Podocarpus fleuryi* Hickel | China, Vietnam | (ePIC, 2009; GRIN, 2009) |
| *Nageia wallichiana* (C. Presl) Kunztee | *Podocarpus walllichianus* C. Presl | China, India, Indonesia, Malaysia, Papua New Guinea, Philippines, Thailand | (ePIC, 2009; GRIN, 2009) |
| *Nageia nagi* (Thunb.) Kunztee | *Agathis veitchii* (Henkel & W. Hochst.) Seward & Ford; *Dunnara veitchii* Henkel & W. Hochst.; *Decussocarpus nagi* (Thunb.) Laub.; *Decussocarpus nagi* var. *formosensis* (Dummer) Silba; *Myrica nagi* Thunb.; *Nageia caesia* (Maxim.) Kunztee; *Nageia cuspidata* (Endl.) Gordon; *Nageia formosensis* (Dummer) C. N. Page; *Nageia grandifolia* (Endl.) Gordon; *Nageia nagi* var. *formosensis* (Dummer) Silba; *Nageia nagi* var. *koshunensis* (Kaneh.) D. Z. Fu; *Nageia nankoensis* (Hayata) R. R. Mill; *Nageia ovata* Gordon; *Podocarpus caesia* Maxim.; *Podocarpus cuspidatus* Endl.; *Podocarpus formosensis* Dummer; *Podocarpus formosensis* var. *koshunensis* (Kaneh.) Merr. & Yamam.; *Podocarpus grandifolius* Endl.; *Podocarpus japonicus* J. Nelson; *Podocarpus kushunensis* (Kaneh.) Kaneh.; *Podocarpus nageia* R. Br. ex Endl.; *Podocarpus nagi* (Thunb.) Pilg.; *Podocarpus nagi* var. *caesia* (Maxim.) Makino; *Podocarpus nagi* (Thunb.) Makino, *Podocarpus nagi* | China, Japan, Taiwan | (Facciola, 1990; Huxley, 1992; GRIN, 2009) |
Podocarpus caparadoni de Laub.

Podocarpus costalis C. Presl

Nageia costalis (C. Presl) Kuntze;
Podocarpus costalis var. taiwanensis Gaussen

Podocarpus cunninghamii Colenso

Nageia hallii (Kirk) Kuntze; Podocarpus hallii Kirk;
Podocarpus totara var. hallii (Kirk) Pilg.

Podocarpus elongatus (Aiton) L’Hér.

Nageia elongata (Aiton) F. Muell.; Podocarpus thunbergii var. angustifolia; Taxus capensis Lam.; Taxus elongata Aiton

Podocarpus fasciculus de Laub.

Podocarpus macrophyllus (Thunb.) Sweet var. liukiuensis Warb.; Podocarpus macrophyllus Sweet f. grandifolia Pilg.

Podocarpus glomeratus

Nageia glomerata (D. Don) Kuntze; Podocarpus cardenasi J. Buchholz & N. E. Gray; Podocarpus rigidus Klotsch ex Endl.

Podocarpus gnidioides Carrière

Podocarpus guatemalensis Standl.

Podocarpus allenii Standl.; Podocarpus guatemalensis var. allenii (Standl.) J. Buchholz & N. E. Gray; Podocarpus guatemalensis var. pinetorum (Bartlett) J. Buchholz & N. E. Gray; Podocarpus pinetorum Bartlett

Podocarpus humbertii

Podocarpus henkelii Stapf ex Dallim. & A. B. Jacks

Podocarpus ensicusulus Melville

Podocarpus javanicus (Burm. f.) Merr.

Bracteocarpus imbricatus (Blume) A.V. Bobrov & Melikyan; Nageia cupressina (R. Br. ex G. Benn.) F. Muell.; Podocarpus cupressinus R. Br. ex G. Benn.; Podocarpus imbricatus Blume; Podocarpus javanicus Merr.; Thuya javanica Burm. f.

Podocarpus lambertii Klotzsch ex Endl.

Podocarpus latifolius (Thunb.) R. Br. ex Mirb.

Podocarpus milanjianus Rendle;
Podocarpus thunbergii Hook.; Taxus latifolia Thunb.

Podocarpus macrophyllus (Thunb.) Sweet

Podocarpus madagascariensis de Laub.

Podocarpus alpinus R. Br. ex Hook. f.

Australia; New South Wales, Victoria and Tasmania

Podocarpus caparadoni de Laub.

Madagascar

Podocarpus costalis C. Presl

Philippines, Taiwan

Podocarpus Cunninghamii Colenso

New Zealand

Podocarpus elongatus (Aiton) L’Hér.

South Africa

Podocarpus fasciculus de Laub.

Japan, Taiwan

Podocarpus glomeratus

Ecuador, Bolivia, Peru

Podocarpus gnidioides Carrière

Australia, Costa Rica, India, Malaysia, Philippines, New Caledonia, New Britain, New Zealand, South America

Podocarpus guatemalensis Standl.

Belize, Colombia, Costa Rica, Ecuador, Guatemala, Honduras; Nicaragua, Panama

Podocarpus humbertii

Madagascar

Podocarpus javanicus (Burm. f.) Merr.

South Africa, Tanzania

Podocarpus lambertii Klotzsch ex Endl.

Argentina, Brazil

Podocarpus latifolius (Thunb.) R. Br. ex Mirb.

Angola, Cameroon, Kenya, Malawi, Mozambique, Nigeria, South Africa, Sudan, Swaziland, Uganda, Zaire, Zambia, Zimbabwe

Podocarpus macrophyllus (Thunb.) Sweet

Australian: Tasmania, Victoria and New South Wales

Podocarpus alpinus R. Br. ex Hook. f.; Podocarpus alpinus R. Br. ex Mirbel; Podocarpus acutifolius Kirk;
Podocarpus alpinus var. lawrencei (Hook. f.) Hook. f.

Podocarpus macrophyllus (Thunb.) Sweet

Japan, Taiwan

Podocarpus madagascariensis de Laub.

Madagascar

Podocarpus alpinus R. Br. ex Hook. f.; Podocarpus nagi var. ovatus (Gordon) Makino; Podocarpus nankoensis Hayata;
Podocarpus ovatus (Gordon) Henkel & W. Hochst.

(continued on next page)
| Species name | Synonym | Geographical distribution | References |
|--------------|---------|---------------------------|------------|
| Podocarpus neriifolius D. Don | Margbensonia neriifolia (D. Don) A. V. Bobrov and Melikyan; Nageia discolor (Blume) Kuntze; Nageia endlicheriana (Carrière) Kuntze; Nageia leptostachys (Blume) Kuntze; Nageia neglecta (Blume) Kuntze; Nageia neriifolia (D. Don) Kuntze; Podocarpus decipiens N. E. Gray; Podocarpus discolor Blume; Podocarpus endlicherianus Carrière; Podocarpus junghuhniannus Miq.; Podocarpus leptostachys Blume; Podocarpus macrophyllus var. acuminatissima E. Pritz.; Podocarpus neglectus Blume; Podocarpus neriifolius var. decipiens (N. E. Gray) Silba; Podocarpus neriifolius var. membranaceus Wasscher; Podocarpus neriifolius var. penibukanensis Silba; Podocarpus neriifolius var. polyanthus Wasscher; Podocarpus neriifolius var. staintonii Silba; Podocarpus polyanthus (Wasscher) Gaussen | India, Indonesia, Laos, Nepal, Papua New Guinea, Philippines, Thailand | (Farjon, 2001; GRIN Taxonomy of Plants, 2009) |
| Podocarpus nivalis Hook. | Nageia nivalis (Hook.) Kuntze; Podocarpus montanus Colenso; Podocarpus nivalis var. erectus Cockayne | New Zealand | (Farjon, 1998; GBIF, 2009; GRIN, 2009) |
| Podocarpus nubigenus Lindl. | Nageia nubigena (Lindl.) F. Muell. | Chile, Argentina | (Bisby et al., 2008; GRIN, 2009) |
| Podocarpus oleifolius D. Don | Nageia macrostachya (Parl.) Kuntze; Nageia oleifolia (D. Don) Kuntze; Podocarpus macrostachys Blume; Podocarpus monteverdeensis de Laub.; Podocarpus oleifolius var. costaricensis J. Buchholz & N. E. Gray; Podocarpus oleifolius var. equadorensis Silba; Podocarpus oleifolius var. macrostachys (Parl.) J. Buchholz & N. E. Gray; Podocarpus oleifolius var. trujillensis J. Buchholz & N. E. Gray | Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Panama, Peru, Venezuela, | (Bisby et al., 2008; GRIN, 2009) |
| Podocarpus parlatorei Pilg. | Nageia angustifolia (Parl.) Kuntze; Podocarpus angustifolius Parl. | Argentina, Bolivia, Peru | (Bisby et al., 2008; GRIN, 2009) |
| Podocarpus pendulifolius | Podocarpus celebicus Warb.; Podocarpus pilgeri var. thailandensis Gaussen; Podocarpus schlechteri Pilg.; Podocarpus tixieri Gaussen; Podocarpus wangii C. Chang | Venezuela | Bisby et al. (2008) |
| Podocarpus pilgeri Foxw. | Podocarpus celebicus Warb.; Podocarpus pilgeri var. thailandensis Gaussen; Podocarpus schlechteri Pilg.; Podocarpus tixieri Gaussen; Podocarpus wangii C. Chang | China, Papua New Guinea, Philippines | Bisby et al. (2008) |
| Podocarpus purdieanus Hook. | Nageia purdieana (Hook.) F. Muell.; Podocarpus jamaicensis Hort. | Jamaica | (Silba, 1986; Bisby et al., 2009) |
| Podocarpus rostratus Laurent | Podocarpus rostratus var. perrieri (Gaussen & Woltz) Silba | Madagascar | Bisby et al. (2008) |
| Species                                      | Common Name | Location          | Authors            |
|----------------------------------------------|-------------|-------------------|--------------------|
| Podocarpus salignus D. Don                   | Nageia chilina (Rich.) F. Muell.; Podocarpus chilinus Rich. | Chile              | Bisby et al. (2008) |
| Podocarpus sellowii var. Sellowii Klotzsch ex Endl. |             | Brazil            | Bisby et al. (2008) |
| Podocarpus sellowii var. angustifolius Pilg   |             | Brazil            | Bisby et al. (2008) |
| Podocarpus smithii de Laub.                  |             | Australia, Peru   | Farjon et al. (1993) |
| Podocarpus spruce                            | Nageia totara (D. Don) Kuntze; Podocarpus hallii (T. Kirk.); Podocarpus totara var. waihoensis | New Zealand        | Bisby et al. (2008); GBIF, 2009; GRIN, 2009 |
| Podocarpus totara G. Benn. Ex D. Don          |             | Brazil            | Bisby et al. (2008) |
| Podocarpus transiens                         | Prumnopitys amara (Blume) de Laub. Podocarpus andinus (Poepp. Ex Endl.) de Laub. Prumnopitys ferruginea (D. Don) de Laub. | Brazil             | Bisby et al. (2008) |
| Prumnopitys ferruginea (D. Don) de Laub.     | Nageia ferruginea (G. Benn. ex D. Don) F. Muell.; Podocarpus ferruginous D. Don; Stachycarpus ferruginous (G. Benn ex D. Don) Tiegh. | New Zealand        | Bisby et al. (2008); GRIN (2009) |
| Prumnopitys ferruginoides (Compton) de Laub. | Podocarpus distichus J. Buchholz; Podocarpus distichus var. maialis J. Buchholz; Podocarpus ferruginoides Compton | New Caledonia      | Bisby et al. (2008); GRIN, 2009 |
| Prumnopitys ladei (F. M. Bailey) de Laub. Prumnopitys montana (Humb. & Bonpl. ex Willd.) de Laub. Prumnopitys taxifolia (Sol. ex D. Don) de Laub. | Podocarpus ladei F.M. Bailey Taxus montana, Podocarpus taxifolia H.B.K. Dacrydium mai A. Cunn.; Dacrydium taxifolium Banks & Sol. Ex D. Don; Nageia spicata (R. Br.) F. Muell.; Podocarpus spicatus R. Br. ex Hook. Stachycarpus spicatus (R. Br.) Tiegh. | Australia, Colombia, Ecuador, Peru, Venezuela | Bisby et al. (2008); Silba (1986) |
| Prumnopitys taxifolia (Sol. ex D. Don) de Laub. |             | New Zealand       | Farjon, 2001; GBIF, 2009; GRIN, 2009 |
| Retrophyllum comptonii (J. Buchholz) C. N. page | Decussocarpus comptonii (J. Buchholz) de Laub.; Nageia comptonii (J. Buchholz) de Laub.; Podocarpus comptonii J. Buchholz | New Caledonia      | GBIF, 2009; GRIN, 2009 |
| Retrophyllum vitiensis (Seem.) C. N. Page     | Decussocarpus vitiensis (Seem.) de Laub.; Nageia vitiensis (Seem.) Kuntze; Podocarpus filicifolius N. E. Gray; Podocarpus vitiensis Seem. | Fiji, Indonesia, Papua New Guinea, Solomon Islands | Bisby et al. (2008); GBIF, 2009; GRIN, 2009 |
| Sundacarpus amarus (Blume) C.N.Page           | Nageia amara (Blume) F. Muell.; Nageia eurhyncha (Miq.) Kuntze; Podocarpus amarus Blume; Podocarpus eurhyncha Miq.; Podocarpus pedunculatus F. M. Bailey; Prumnopitys amara (Blume) de Laub.; Stachycarpus amarus (Blume) Gaussen | Australia, Malesia | Bisby et al. (2008) |
Table 2
A summary of non-medicinal uses of *Podocarpus* s.l. species.

| Species                          | Geographical distribution | Uses                                                                                       | References                                      |
|---------------------------------|---------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------|
| *Podocarpus amara* Blume        | Java, Sumatra, Philippines, Queensland | The wood is used locally for posts, boards, beams and house construction.                 | (Uphof, 1968; Usher, 1974)                      |
| *Podocarpus blume* Endl.        | Java, Papua New Guinea, Peninsula, Cambodia, Malaysia and Philippines | The wood is beautifully grained and is used for interior work and panels.                | (Uphof, 1968; Usher, 1974)                      |
| *Podocarpus coriaceus* Rich.    | West Indies, Venezuela and Colombia | The yellowish wood is used for carving and carpentry.                                       | (Uphof, 1968; Usher, 1974)                      |
| *Podocarpus dacrydioides* Rich. Kahika. | New Zealand | The light coloured wood is used for framing houses, panels and interiors, furniture, boxes and boat building. It is also used for paper pulp. The fruits are eaten locally. | (Uphof, 1968; Usher, 1974)                      |
| *Podocarpus elongatus* R. Br. Ex Endlener | Queensland, New South Wales | The wood is light, tough, silky, close-grained, easily worked and not readily attacked by teredo and termites. It is used for making furniture. The fleshy stems and fruits are eaten by the Aborigine. | (Uphof, 1968; Usher, 1974; Cribb and Cribb, 1981) |
| *Podocarpus falcatus* (Thunb.) R. Br. Ex Mirb. | South Africa | The bark is used for magical purposes. It is burned in the kraal as a charm to prevent the cattle from straying. The wood is extensively used for furniture, roof beams, floorboards and window frames. It is considered as one of the best woods for boat building. The bark contains 3–6% tannin and is used for tanning leather and the ripe fruits are edible but very resinous. | (Beentje, 1994; Hutchings et al., 1996; Venter and Venter, 1996; Arnold et al., 2002) |
| *Podocarpus ferrugineus* Don. (Miro) | New Zealand | The hard, tough wood is used for frames of houses, furniture making, and in turnery.       | (Uphof, 1968; Usher, 1974)                      |
| *Podocarpus guatemalensis* Standl. | Mesoamerica, S.W. America | This tree is used as a source of wood.                                                     | Wiersema and León (1999)                        |
| *Podocarpus Hallii* Kirk.        | New Zealand | The wood is close-grained, firm, dull-red, resistant to teredo worms and is used for piers, wharves and building ships. | (Uphof, 1968; Usher, 1974)                      |
| *Podocarpus henkelii* Stapf ex Dallim. & Jacks. | South Africa | The tree is used as a source of timber and for ornamental purposes. The bark is used for magical purposes and as a love charm. It is chewed and spat out into the wind as the name of the loved one is repeated. | (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Wiersema and León, 1999; Arnold et al., 2002) |
| *Podocarpus imbricatus* Blume    | Malaysia | The beautiful grained wood is used for interior work.                                       | (Uphof, 1968; Usher, 1974)                      |
| *Podocarpus latifolius* (Thunb.) R. Br. Ex Mirb. | South Africa, East Africa | In South Africa, this species is one of the principal timbers mostly used in small-scale furniture workshops. It makes a | (Van der Merwe, 1998; Wiersema and León, 1999; Arnold et al., 2002) |
substantial contribution to the local economy creating about 500 jobs and is worth R 16 million annually. It is also used as wood in East Africa. It is used for magical purposes in South Africa. (Mabberley, 1997; Wiersema and León, 1999)

**Podocarpus macrophyllus** (Thunb.) Sweet

China, Japan, E. Asia

The wood is used for timber and the tree is planted for ornamental purposes. (Mabberley, 1997; Wiersema and León, 1999)

**Podocarpus madagascariensis** Baker

Madagascar

The wood is used locally for carpentry and building houses. (Uphof, 1968; Usher, 1974)

**Podocarpus nagi** (Thunb.) Zoll. & Moritz

East Asia, Japan, Mexico, New Zealand

The seeds yield edible oil which is also used in industry (no specification of the industry), and the young leaves are parboiled and eaten. In Himalayas, the fruits are sold in local markets and the wax used to make aromatic candles and soaps. (Weiner, 1980; Faciola, 1990)

**Podocarpus neriifolius** D. Don.

Papua New Guinea, Himalayas and China

The light yellowish hard wood is used for carpentry in Burma. The fleshy receptacle of fruits is eaten locally in Nepal. It is also used as ornamental. (Uphof, 1968; Usher, 1974; Wiersema and León, 1999)

**Podocarpus nivicus**

Japan

The tree is used as hedges and the fruits are edible (raw or cooked). Sweet and pleasant to taste. (Crowe, 1990; Mabberley, 1997)

**Podocarpus nubigenus** Lindl.

South America

This species is used for wood and as an ornamental. Wiersema and León (1999)

**Podocarpus oleifolius** D. Don.

Bolivia and Costa Rica

The yellowish wood is used for carving and carpentry. (Uphof, 1968; Usher, 1974; Wiersema and León, 1999)

**Podocarpus rumphii** Blume

Malaysia, Archipelago

The light yellow wood is easy to work, is not attacked by borers and is used locally for houses, boats and turning. (Uphof, 1968; Usher, 1974)

**Podocarpus salignus** D. Don.

South America

The watery sap is drunk or used in the preparation of a beer-like beverage; the young shoots are made into a beverage resembling spruce beer and the fruits are edible with a sweet flavor. It is also used as ornamental. (Crowe, 1990; Faciola, 1990; Wiersema and León, 1999)

**Podocarpus spicata** R. Br.

New Zealand

This species is an important commercial timber. It is used for building houses, bridges, ballroom floors and railway sleepers. (Uphof, 1968; Usher, 1974)

**Podocarpus spinulosa** R. Br.

Queensland

The fruits, the size of a plum are used locally for jams and preserves. (Uphof, 1968; Usher, 1974)

**Podocarpus taxifolia** H.B.K.

South America

The wood is used locally especially in Colombia for furniture making. (Uphof, 1968; Usher, 1974)

**Podocarpus thunbergii** Hook.

Central and southern Africa

The bright yellow wood is used for furniture making, building of coaches and wagons. (Uphof, 1968; Usher, 1974)

**Podocarpus totara** G. Bennett ex D. Don

New Zealand

The deep-red wood is durable and teredo resistant. It is used by the Maoris for canoes, carpentry, building rafters, rail-road, telegraph poles, bridges, wharves, construction works where spans are required. The tree is planted as ornamental and the fruits are edible, sweet and juicy but with a turpentine taste. (Uphof, 1968; Usher, 1974; Crowe, 1990; Mabberley, 1997; Wiersema and León, 1999)
## Table 3
A summary of medicinal uses of *Podocarpus* s.l. species.

| Species                        | Geographical distribution | Medicinal uses                                                                 | References                                                                 |
|--------------------------------|---------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| *Podocarpus henkelii* Stapf ex Dallim. & Jacks. | South Africa | The sap was used for chest complaints by woodmen working in southern African forests. | (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996) |
| *Podocarpus falcatus* (Thunb.) R. Br. Ex Mirb. | South Africa, East Africa | The bark is used as herbal remedies to treat animal diseases such as gallsickness in cattle and distemper in dogs. The sap is used as a remedy for chest complaints and the oils are said to have medicinal properties in curing gonorrhoea. The powder from the bark is used for curing headaches. Unknown part is used for stomachache and cattle diseases. | (Watt and Breyer-Brandwijk, 1962; Sindiga, 1995; Hutchings et al., 1996; Venter and Venter, 1996; Pankhurst, 2000; Dold and Cocks, 2001) |
| *Podocarpus ferrugineus* Don. (Miro) | New Zealand | The species is said to have medicinal uses, but how or what is used for has not been specified. However, in Uphof, 1968, the gum is mentioned to be used in medicine. | (Uphof, 1968; Johnson, 1999) |
| *Podocarpus latifolius* (Thunb.) R. Br. Ex Mirb. | South Africa, East Africa | The bark is used to treat a variety of animal diseases including distemper in dogs and gallsickness in cattle in central eastern Cape Province. The Maasai of East Africa use the bark decoction as a remedy for stomachache. The sap was used by woodmen working in southern African forests for chest complaints In Tanzania, in early 1970s, bark material was gathered and extracts prepared and screened for activity against diseases such as cancer and AIDS. | (Watt and Breyer-Brandwijk, 1962; Cunningham, 1993; Beentje, 1994; Sindiga, 1995; Hutchings et al., 1996; Dold and Cocks, 2001) |
| *Podocarpus macrophyllus* (Thunb.) Sweet | China, Japan, E. Asia | The stem bark is used in the treatment of worms (e.g. ringworms) and blood disorders. A decoction of the fruit is used as a tonic for the heart, kidneys, lungs and stomach. | Duke and Ayensu (1985) |
| *Podocarpus nagi* (Thunb.) Zoll. & Moritz. | East Asia, Japan, Mexico, New Zealand | The bark is used traditionally as an antiseptic, astringent, carminative and in the treatment of fevers, asthma and coughs. The bark is mixed with ginger and is used as a rubefacient in the treatment of cholera. The stem bark is used as a wash in the treatment of arsenic poisoning, skin diseases and ulcers. The fruit is carminative, pectoral and stomachic. The seed is used in the treatment of cholera, heart ailments, stomach diseases and sweaty feet. | (Chopra et al., 1986; Duke and Ayensu, 1985) |
| *Podocarpus nakaii* Hayata | Taiwan | A very popular plant in eastern medicine as an antitumor agent and pest control. It is commonly known as the Chinese antitumor remedy and it’s locally called ‘Pai-ju-chin’. | Nakanishi (2006) |
| *Podocarpus nerifolius* D. Don. | Papua New Guinea, Himalayas and China | A decoction of the leaves is used in Ayurvedic medicine for the treatment of rheumatism and painful joints. | Chopra et al. (1986) |
| *Podocarpus totara* G. Bennett ex D. Don | New Zealand | Its use in Maori medicines dates back to at least 100 years. Smoke for the shavings from the bark is used to treat venereal diseases such as gonorrhoea and syphilis. A hole is dug in the ground and a small smoky fire is made, the smoke escapes by the shaft over which the patient sits covered with a sheet or old cloak. The strips from the bark are used as splints on broken limbs and this use dates back to 1869. The leaves are used to treat piles, sores and lesions. The berries are consumed as a laxative and also to treat constipation in women. A decoction from the inside of the bark is used to reduce fever. | Riley (1994) |
| *Podocarpus sp.* | Java, Malaya | Used to treat arthritis and rheumatism. Action: anodyne. | Johnson (1999) |
venereal diseases such as gonorrhoea and syphilis. The use of
strips from the bark as splints on broken limbs dates back to
1869. Leaves and smoke from the leaves is used to treat piles,
sores and lesions. The berries are consumed as a laxative and
unknown parts of the plant to treat constipation (titakiki) in
women. A decoction from the inside of the bark is used to
reduce fever, particularly uncontrolled fever (Riley, 1994). In
Uphof (1968) and Johnson (1999), it is mentioned that the gums
of Podocarpus ferrugineus D. Don are used in medicine, but
how and who uses it is not indicated. Unknown Podocarpus
species in Java and Malay are used to treat arthritis and
rheumatism and also used as an anodyne (Johnson, 1999).

The stem bark of Podocarpus macrophyllus D. Don is used
in the treatment of worms (especially ringworm) and blood
disorders (Duke and Ayensu, 1985) in Ayurvedic medicine. A
decoction of the fruit is used as a tonic for the heart, kidneys,
lungs and stomach (Duke and Ayensu, 1985). P. nertifolius is
used in traditional medicine in Asia. A decoction of the leaves
is used in Ayurvedic medicine for the treatment of rheumatism
and painful joints (Chopra et al., 1986). Podocarpus nakaii
Hayata is very popular in eastern medicine as an antitumor
agent and in pest control. It is commonly known as the Chinese
antitumor remedy and it is locally called ‘Pai-ju-chin’
(Nakanishi, 2006).

The bark of P. henkelii and P. latifolius is widely used in
Zulu traditional medicine in South Africa (Hutchings et al.,
1996). The bark of P. latifolius and P. falcatus are used as
herbal remedies to treat a variety of animal diseases including
distemper in dogs and gall sickness in cattle in central Eastern
Cape Province (Dold and Cocks, 2001; Masika and Afolayan,
2003). Woodsmen working in southern African forests are
reported to use the sap from these trees for chest complaints
(Watt and Breyer-Brandwijk, 1962). A bark decoction of P. latifolius is also used by the Maasai in Kenya as a remedy
for stomach ache (Beentje, 1994). Unspecified communities in
East Africa use P. latifolius and P. falcatus to treat stomach
ache and cattle diseases (Sindiga, 1995). In Ethiopia P. fal-
catus oils are said to have medicinal properties in curing
gonorhoea and the powder from the bark is used for curing
headaches (Pankhurst, 2000). In the 1970s, in a span of two
weeks 150 kg bark material of Podocarpus milanjianus Rendle
(P. latifolius) was gathered in Tanzania. These extracts were
prepared and screened for activity against diseases such as
cancer and Acquired Immuno-Deficiency Syndrome (AIDS)
(Cunningham, 1993).

3. Phytochemistry

Since the early 1900s, the chemical constituents of some
species of Podocarpus have been extensively investigated
(Kubo and Ying, 1991). Phytochemical studies of a number of
species have led to the isolation and elucidation of various
terpenoids and nor- and dindoriterpenoid dilactones (Ito and
Kodama, 1976; Hayashi et al., 1979). Biflavonoids of the
amentoflavone and hinokiflavone groups are present in the great
majority of Podocarpus species, and together with nor- and bis-
norditerpenes these are said to be taxonomic markers of this

Podocarpus and Juniperus are the two genera of gymnosperms known to be
isoflavonoid producers (Dewick, 1994). The classes of some of the
compounds isolated from species of Podocarpus s.l. and the
new revised genera, including their pharmacological activities
are summarised in Fig. 1. Norditerpene dilactones (1–23) are
the most common and are present amongst most of the species
of Podocarpus investigated so far. Some of the diterpene
dilactone glycosides contained one sugar moiety (1–2), while
other glycosides contain a disaccharide moiety (3–5) (Xuan
et al., 1995).

Flavonoid (24–27) types are also very common including
monoflavonoids, biflavonoids and flavonoid glycosides. The
presence of methoxyl and hydroxyl groups in these biflavonoids
and monoflavonoids play an important role in mediating
cytotoxic activity observed by these compounds (Kuo et al.,
2008). Markham et al. (1985) investigated the distribution of
flavonoids in the New Zealand Podocarpus species and sugges-
ted that the occurrence pattern of major compound
types clearly showed correlation with the newer taxonomy. The
major flavonoids were C-glycosylflavonones, flavonol 3-O-
glycosides, flavonol 3-methylether glycosides and dihydrofla-
vonol glycosides (Markham et al., 1985). Totarol diterpenes and
semperviol-type diterpenes (28–39) have been isolated from
various species of Podocarpus and segregated genera
(Shapiro and Guggenheim, 1998; Nicolson et al., 1999; Evans
and Furneaux, 2000; Sato et al., 2008). Diterpenes of the abietane
chemical class (42–48) have also been isolated from several
species (Becerra et al., 2002). Ponasterone A (49), a
phytoecdysterone that inhibits ecdysis in insects was isolated
and described from P. nakaii (Nakanishi et al., 1966). Taxol
(50), a tubulin binding diterpene originally isolated from Taxus
brevifolia, has been discovered in P. gracilior Pilger (Stahlhut
et al., 1998).

A number of compounds isolated from Podocarpus s.l. have
been found to be unique amongst the conifer families to
Podocarpaceae. For example ponasterones A, B, C and D, and
podecdysone B isolated from P. nakaii. These compounds are
known to be ecdysone receptor agonist disrupting the life cycle
of insects/herbivores. Another unique compound to this genus
is nagilactone C which is cytotoxic to a number of cancer cell
lines. Amentoflavone and (-)-epicatechin (flavan-3-ol) have
been isolated from a number of families, but amongst conifers,
they are only known to occur in Podocarpaceae. Amentoflavone
has been isolated from Anacardiaceae, Caprifoliaceae, Cyca-
daceae and Ginkgoaceae. This compound is a potent inhibitor of
nucleotide phosphodiesterase and a cyclooxygenase inhibitor. It
shows antifungal activity against growth of Aspergillus
fumigatus, Botrytis cinerea and Trichoderma glaucum. Ament-
oflavone is an agonist of the central GABA_{A}R benzodiazepine
receptor, hence exhibiting anticonvulsant and anxiolytic
activity. (-)-Epicatechin has been isolated from Hippocastana-
ceae, Fabaceae, Rosaceae, Podocarpaceae and Theaceae. This
compound has antibacterial, anti-hyperglycaemic, anti-inflam-
matory, antimutagenic and antiperoxidative activities. In vivo
studies have shown that this compound activates dopamine
receptors which are involved in schizophrenia and Parkinson’s
Fig. 1. Chemical structures and pharmacological activities of some compounds isolated from species of *Podocarpus* and revised genera. \(^1\)antibacterial; \(^2\)antifungal; \(^3\)antitumor/cytotoxic/anticancer; \(^4\)plant growth regulatory; \(^5\)insect growth regulatory; \(^6\)anti-inflammatory; \(^7\)insecticidal; \(^8\)antioxidant; \(^9\)molluscicidal; \(^10\)larvicidal; \(^11\)gastroprotective; \(^12\)hypocholesterolemic; \(^13\)anti-tyrosinase/melanin inhibition.
Fig. 1 (continued).

Podocataphlavone A (23)

Podolactone C (21)¹

Podolide (22)², ³

2α-hydroxyxynylactone

Podophyllone (24)

Amentolavone (25)

4β-carboxy-19-nortotalol (30)¹

Totarol (29)¹, ¹²

Totarolone (31)¹

2,3-dihydro-4', 4'-di-O-methylmentholavone (27)¹³

Hevealavone (26)

Totakwilol H (39)¹

Inumakiol G (33)¹

Inumakiol B (33)¹

Inumakiol A (32)

Inumakiol F (37)¹

Inumakiol E (36)

Inumakiol C (34)

Inumakiol D (35)

Inumakiol H (39)¹

Macrophylic acid (40)¹
Fig. 1 (continued).
4. Biological activity

Coniferous plants are rich in abietene type of diterpenes which provide an interesting source of biologically active agents, thus the need to utilize this taxonomic group. *Podocarpus* s.l. contains certain secondary metabolites unique in their structure and pharmacological properties. Early scientists considered these secondary metabolites of no interest. Later they realized that these compounds were bioactive principles, which are involved in complex interactions such as symbiosis, resistance and defence against diseases. This genus is rich in diterpenoids (Ito and Kodama, 1976), with several biological activities including antitumor, antimicrobial, plant growth regulatory, insect growth regulatory and herbivorous mammalian antifeedant activities and the most common compounds are nor- and bis-norditerpene dilactones (Geran et al., 1972; Brown and Sanchez, 1974; Hayashi et al., 1992; Zhang et al., 1992; Kubo et al., 1993; Park et al., 2003).

4.1. Anticancer/cytotoxic activities

Norditerpenes and totarol from *Podocarpus* are known to have cytotoxic activities against several forms of cancer including, P388 murine leukemia cells (Park et al., 2003, 2004). Nagilactone C isolated from *P. totara* and *P. nerifolius* has potent antiproliferative activity against human fibrosarcoma and murine colon carcinoma tumour cell lines exhibiting ED50 values of 2.3 and 1.2 µg/ml (6.0 and 3.2 µM) respectively (Shrestha et al., 2001). These values fall in the range of a significant cytotoxic agent i.e. ED50 ≤ 4 µg/ml (Geran et al., 1972). In another experiment the cytotoxic activity of nagilactone C was more potent against human fibrosarcoma cells than the positive control 5-fluorouracil (ED50 = 8.0 µM), a clinically used drug for the treatment of human tumours (Frank and Teich, 1997). Nagilactone F and nagilactone G found in *P. milanjianus* Rendle and *Podocarpus sellowii* Klotzsch ex Endl. exhibited in vivo activity against P388 and in vitro activity against 9 KB cell lines (Hembree et al., 1979).

Taxol, isolated from *P. gracilior* Pilger inhibits the growth of HeLa cells (human cancer cells) and is a promising new treatment for several forms of cancer (Stahlhut et al., 1998). It may be useful to assay for taxol in other members of the genus *Podocarpus* s.l. as a source for commercial production. Totarol, a diterpenoid from a number of *Podocarpus* s.l. has displayed antitumor activity against the 9 KB cell system with an ED50 of 4.9 µg/ml (Hembree et al., 1979). Cytotoxic activity was exhibited by totarol against three human proliferative cell lines (CH2983, HeLa and MG63) at concentrations over 30 µmol/L (Evans et al., 1999).

Purdilactone A, B and C isolated from the alcoholic extracts of *Podocarpus purdieanus* Hook. exhibited in vitro cytotoxicity in 9PS mouse lymphocytic leukemia and in human tumor cell lines A-549 (lung carcinoma), MCF-7 (breast adenocarcinoma) and HT-29 (colon adenocarcinoma) (Wang et al., 1997). Methyl-13-hydroxy-14-isopropyl-9(11), 12, 14(8)-podocarpatriene-19-oate, 19-hydroxytotarol, totaradiol and 4beta-carboxy-19-nor-totarol isolated from root and bark extracts of *Podocarpus madagascariensis* Baker exhibited cytotoxic activity against the A2780 ovarian cancer cell line (Reynolds et al., 2006).

Rakanmakilactones A–F, sulfur-containing norditerpene dilactones isolated from leaves of *P. macrophyllus* var. maki Endl. exhibited a potent cytotoxic effect against P388 murine leukemia cells in a dose–response curve with IC50 values of 0.31, 0.18, 0.29, 0.25, 5.0 and 4.3 µg/ml, A–F respectively (Park et al., 2004). The cytotoxic assays were performed using the MTT assay method and the cells were incubated for 48 h. The compounds were tested in various concentrations ranging from 100 to 0.1 µg/ml and DMSO was used as the control (Park et al., 2004).

Podolactone D from leaves of *P. macrophyllus* var. maki has shown moderate cytotoxic activity on P388 murine leukemic cells with S50-Podolactone D giving an IC50 value of 0.52 µg/ml and S50-Podolactone D giving 0.23 µg/ml (Park et al., 2003). Podolide (antileukemic norditerpene dilactone), is the first compound of this class reported to show tumor-inhibitory activity. This compound was responsible for the tumor-inhibitory activity of an ethanol extract of the twigs and leaves of *P. gracilior*. It also occurs in *P. falcatus* (Kupchan et al., 1975).

Recently, 95% ethanolic extract of the stems and leaves of *Podocarpus fasciculus* de Laub. exhibited cytotoxicity against several human tumor cell lines in vitro (Kuo et al., 2008). Thirty two compounds from this species were evaluated for cytotoxicity against human KB, HeLa, Hepa, DLD and A-549 tumor cell lines using the MTT assays. The cells and the samples in four different concentrations (not indicated) were incubated at 37 °C for three days before the addition of MTT for
5 h. Nagilactone C showed the most potent cytotoxicity against DLD cells (ED$_{50}$=2.57 µg/ml), heaveaflavone, podocarpusflavone-A and II-4", 1-7-dimethoxyamentoflavone showed moderate cytotoxicity (ED$_{50}$ ca. 4-14 µg/ml) against the human tumor cell lines, apigenin and kemperförl showed inhibitory effects on DLD tumor cells (ED$_{50}$=5.48 µg/ml and ED$_{50}$=18.39 µg/ml respectively). The preliminary structure-activity relationship studies suggested the methoxyl and hydroxyl groups in biflavonoids and monoflavonoids respectively, play a crucial role in mediating cytotoxic activity (Kuo et al., 2008).

4.2. Antimicrobial activity

Totarol is a potent antibacterial agent which has been isolated from several species of *Podocarpus* s.l. This compound is a broad spectrum antibacterial agent and active against β-lactam resistant strains of bacteria and, either alone or in combination with other molecules, may prove useful in antimicrobial chemotherapy, since its cytotoxicity toward human cell cultures is relatively mild (Muroi and Kubo, 1996; Evans et al., 1999). Totarol$^{TM}$, the commercially produced product of totarol was not cytotoxic on human epidermal keratinocytes (Micol et al., 2001). Totarol is active against *Streptococcus mutans* (Muroi and Kubo, 1996; Moorhead and Bigwood, 2003), penicillin resistant *Streptococcus pneumoniae* (Evans et al., 2000), Erythromycin-resistant *Streptococcus pyogenes*, high-level-gentamicin-resistant *Enterococcus faecalis* (Evans et al., 2000), vancomycin-resistant *E. faecalis*, *Salmonella menston*, *Escherichia coli*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Brevibacterium ammoniagenes* and *Propionibacterium acnes* (Moorhead and Bigwood, 2003). Totarol has been clinically used in the form of an alcohol-based topical medication followed by a totarol-containing moisturiser, for the treatment of acne vulgaris in a 14 year old male with a 14 month history. There was apparent reduction in inflammation, size and extent of lesions over the six week period (David and Daniel, 2006). A skin irritation test of 0.05% totarol solution on 50 human subjects showed no evidence of toxic effects on the skin. In addition to this, totarol is not cytotoxic at concentrations required for antibacterial and antioxidant activity in cosmetic applications. However, above these concentrations it can cause cell damage (David and Daniel, 2006).

The antibacterial and efflux pump inhibitor (EPI) activity of totarol was determined using different strains of *Staphylococcus aureus*. Totarol was assayed at half MIC value in microdilution assays and reserpine was used as a control. Checkerboard combination studies using ethidium bromide (EtBr) and totarol were also performed. Totarol exhibited good antibacterial activity giving an MIC value of 2 µg/ml against *S. aureus* ATCC 25923 and effluxing strains. EtBr MICs for NCTC 8325-4, SA-K1758 (norA null), SA-K3090 and SA-K3092 were 6.25, 0.63, 0.63 and 100 µg/ml respectively, demonstrating the marked increase in EtBr MIC associated with norA over expression. The totarol MIC values for these strains were 2.5, 1.25, 16 and 16 µg/ml, respectively, indicating that totarol is not a substrate for NorA (Smith et al., 2007). The modulatory activity of totarol against effluxing strains at half MIC value was comparable to that seen for reserpine. A totarol-mediated eightfold reduction in the MIC value of erythromycin against strain RN4220 was observed whereas reserpine had no activity as a modulator against this strain. Totarol inhibited EtBr efflux by 50% at 15 µM or 4.29 µg/ml, approximately one-fourth of the MIC value for this strain. However, reserpine was a more efficient inhibitor with an IC$_{50}$ of 8 µM. From these findings one can suggest that totarol is a NorA EPI as well as an antistaphylococcal antimicrobial agent. Various reductions in the MIC value of meticillin against MRSA strains have been reported when used with totarol at half of the MIC. At least an 8-fold reduction in the MIC, from >32 to 4 µg/ml was noted by Nicolson et al. (1999) but Muroi and Kubo (1996) observed a 16-fold reduction against one MRSA strain. When totarol was assayed against the clinical isolate EMRSA-15, a 50-fold potentiation of oxacillin activity was observed (Smith et al., 2007). These activities are a clear example of synergy between components of medicinal plants described at a molecular level. Due to the development of resistance mechanisms to current antimicrobials, emulating nature’s strategy and looking at the potential antibiotics with multi drugs, resistance pumps can be an effective strategy against drug resistance microorganisms.

Several diterpenes isolated from *Podocarpus nubigena* Lindl. and *Podocarpus saligna* D. Don have shown antibacterial activity in the disc diffusion assay against *S. aureus* and *Pseudomonas* sp. and antifungal activity against *Aspergillus* sp., * Fusarium fujikuroi*, *Fusarium ciliatum*, *Mucor meioi*, *Nematospora coryli*, *Penicillium notatum* and *Paecilomyces variotii* (Becerra et al., 2002). These diterpenes include ferrunigol, hinikoli, hinokione, totarol, totaradiol, totarolone, abietatriene, 6, 7 dehydroferruginol, isopimarol and acetylferuginol. Gentamicin was used as a positive control and the diameter of inhibition against tested bacteria ranged from 20–25 mm while the compounds exhibited stronger antibacterial activity of 7–18 mm diameter of inhibition (Becerra et al., 2002).

Nagilactone E, the most abundant norditerpene dilactone from *P. nagi* showed moderate to weak activity against *Candida albicans*, *Saccharomyces cerevisiae* and *Pityrosporum ovale* with MIC values of 800, 100 and 50 µg/ml, respectively (Kubo et al., 1993). 2α-hydroxynagilactone, a norditerpene dilactone isolated as an antifungal principle from the root bark of *P. nagi* exhibited weak growth inhibition against *S. cerevisiae* (MIC 800 µg/ml) (Kubo and Ying, 1991). These antifungal activities were not potent enough to be considered for practical use; hence they were examined for synergism effects by combining it with Amphotericin B and anethole in order to enhance activity. This kind of approach seems to be a more promising strategy for efficient utilization of renewable natural substances. At a concentration of 0.78 µg/ml, Amphotericin B enhanced the activity of nagilactone E against *S. cerevisiae* 4-fold, reducing the MIC value from 100 to 25 µg/ml. A reduction of MIC value was also observed against *C. albicans* from 800 to 100 µg/ml. In addition, this enhancement was observed in reverse as well. The MIC value of Amphotericin B against *S. cerevisiae* was lowered from 1.56 to 0.30 µg/ml when combined with 50 µg/ml of
nagilactone E. When 2α-hydroxynagilactone was combined with half the MIC of anethole, the activity against \textit{S. cerevisiae} was enhanced by 128-fold, the MIC value was decreased from 800 to 6.25 µg/ml. The activity of nagilactone E was also increased 128-fold, 16-fold and 32-fold by anethole when tested against \textit{C. albicans}, \textit{S. cerevisiae} and \textit{P. ovale}, respectively. The MIC values were lowered from 800 to 6.25 µg/ml, from 100 to 6.25 µg/ml and from 50 to 1.56 µg/ml, respectively (Kubo et al., 1993). This approach also brings about the effect of synergism, which is a very fundamental mechanism in developing pharmacological agents to treat diseases. Thus researchers should investigate the synergistic properties of natural products and plant extracts independent of the antimicrobial activity they exhibit. This will add to the knowledge base on synergism which is very limited due to few reported studies (Aqil et al., 2005).

Inumakiol B, inumakiol F, inumakiol H, macrophylllic acid, 4β-carboxy-19-nortotarol and lambertic acid isolated from \textit{P. macrophyllus} showed potent antibacterial activities against oral pathogenic microorganisms with MIC values ranging from 3.1 µg/ml to 25 µg/ml. Of these, macrophylllic acid, a totarane diterpene dimer was the most active. The test microorganisms were \textit{S. mutans}, \textit{P. gingivalis}, \textit{P. neriifolius} and \textit{C. albicans} (aerobic bacteria), \textit{Actinomyces viscosus}, \textit{Porphymonas gingivalis}, \textit{Fusobacterium nucleatum} and \textit{Actinobacillus actinomycetemcomitans} (anaerobic bacteria) (Sato et al., 2008). The plates were incubated at 37 °C for 24 h under the aerobic conditions for the aerobic bacteria, for 24 h under anaerobic conditions for \textit{Actinomyces viscosus}, \textit{P. gingivalis} and \textit{A. actinomycetemcomitans} and for 72 h under anaerobic conditions for \textit{F. nucleatum}. Thymol, which was used a reference, gave an MIC value of 100–200 ppm against these bacteria while for these six compounds the MIC values ranged from 25–50 ppm (Sato et al., 2008).

Crude extracts of four South African \textit{Podocarpus} species viz, \textit{P. elongatus}, \textit{P. falcatus}, \textit{P. henkelii} and \textit{P. latifolius} exhibited broad spectrum antimicrobial activity against \textit{B. subtilis} (98 µg/ml), \textit{S. aureus} (98 µg/ml), \textit{E. coli} (390 µg/ml), \textit{Klebsiella pneumoniae} (330 µg/ml) and \textit{C. albicans} (30 µg/ml). The extracts were assayed using the microdilution bioassay described by Eloff (1998) and plates were incubated for 24 h. Neomycin was used as a positive control and it gave an MIC value of 0.07 µg/ml against \textit{B. subtilis}, and 0.26 µg/ml against the other three bacteria (Abdillahi et al., 2008).

These antimicrobial activities provide rational for the traditional uses of some of the species in treating microbial infections such as the use of oils from \textit{P. falcatus} in treating gonorrhoea, sap from \textit{P. falcatus}, \textit{P. henkelii} and \textit{P. latifolius} as a remedy for chest infections (Hutchings et al., 1996; Pankhurst, 2000). The use of the shavings from the bark of \textit{P. totara} in treating venereal diseases and the leaves in treating piles, sores and lesions could be due to the presence of torarol, which is a broad spectrum antibiotic, justifying the use of this species in the Maori medicines (Riley, 1994).

### 4.3. Plant growth inhibitory activity

Since the discovery of plant growth regulatory activities from \textit{Podocarpus} species (Galbraith et al., 1970, 1972; Sasse et al., 1981, 1982; Miller et al., 1984), a number of compounds classified under the norditerpene dilactones and diterpene dilactones such as nagilactones, podolactones and inumakilactones have been isolated. These growth regulatory activities may be attributed to the allelopathic potential of several species of \textit{Podocarpus} s.l. (Macías et al., 2000). Podolactone A significantly decreased the number of mature spikelets of \textit{Lotus temulentum} at a lower concentration than abscisic acid (Sasse et al., 1981). This compound also counteracted the promote effects of gibberelic acid in the barley endosperm bioassay (Sasse et al., 1981), inhibited α-amylase induction in germinating barley (Sasse et al., 1982) and reduced chlorophyll formation in etiolated barley leaves (Miller et al., 1984). At high concentration, podolactone A prevented the induction of α-amylase by gibberelic acid (Sasse et al., 1982).

Podolactone E is considered to be the most potent of all the podolactones (Galbraith et al., 1972; Sasse et al., 1981; cited in Miller et al., 1984). In experiments using barley aged from 6–11 days, 10–11 day old plants were more sensitive to treating with podolactone E. After 8 h exposure to light, further synthesis of protochlorophyll and chlorophyll a was completely inhibited at 10 µM while in controlled tissue the biosynthesis of chlorophyll continued throughout the 22 h exposure to light (Miller et al., 1984). When the light period was extended to 12 h, the effect of podolactone E was detected at a concentration of 0.1 µM and abscisic acid (ABA) also inhibited chlorophyll formation, but was much less effective than podolactone E. After 4 h of light without pre-incubation, 100 µM of podolactone E did not affect ALA synthesis, but showed 50% inhibition after 6 h. With pre-incubation in the dark, ALA formation was completely inhibited immediately after exposure to light. On chlorophyll formation, ABA was more inhibitory than podolactone E at 1 µM on ALA synthesis after dark incubation, but at 10 µM podolactone E was as effective as ABA (Miller et al., 1984). Podolactone A inhibits proton efflux from plant cells induced by fusicoxin without affecting the adenosine triphosphate (ATP) levels. These inhibitions were caused by the suppression of synthesis of protons needed in the porphyrin pathway because podolactones also inhibits gibberelic acid-induced α-amylase formation in barley embryos (Miller et al., 1984; Macías et al., 2000).

Inumakilactone B and podolactone E from \textit{P. nerifolius} exhibited high activity as inhibitors of cell expansion in an assay system employing pea stem segments (Galbraith et al., 1972). These compounds inhibited the growth of the hook and apical segments of pea stems at concentrations of $6 \times 10^{-7}$ M and $10 \times 10^{-7}$ M respectively (Galbraith et al., 1972). Nagilactone E, from \textit{P. nagi} was able to stimulate the growth of cultured cells of \textit{Lactuca sativa} at 0.1 µg/ml and cell wet weight and number per unit wet weight were increased after 14 days incubation. The population of cells treated with this concentration had a higher percentage of cells with shorter cell length compared to the control (untreated). However, at concentrations greater than 1 µg/ml this was not the case and the growth was inhibited rather than stimulated (Tan and Kubo, 1990). Podoandin isolated from methanol leaf extracts of \textit{P. andina} (Poepp. & Endl.) de Laub., completely inhibited the germination of lettuce (\textit{L. sativa}) at
100 mg/l (Kubo et al., 1992). Methanol stem bark extracts of 
P. nagi exhibited plant growth inhibitory activity against lettuce 
seedlings (Kubo and Ying, 1991).

Podolactones A and B are also known to inhibit expansion 
and mitosis of plant cells and their inhibitory activity is equal to 
or greater than that of abscisic acid (Galbraith et al., 1970). 
These podolactones strongly inhibited the growth of hook and 
apical segments of pea stems at a concentration of 2.5×10⁻⁵ M 
and after 24 h. The increase in weight of hook segments as a 
percentage of the control [= 100±11% (mean deviation)] in the 
presence of podolactones A and B was inhibited by 25 and 29% 
respectively (Galbraith et al., 1970). Podolactone A inhibited 
cell division in the Jerusalem artichoke system. Freshly cut 
slices treated with auxin, cytokinin and calcium chloride 
showed a mitotic frequency of 5.7% after 37 h and 7.0% after 
50 h. Addition of podolactone A (2.5×10⁻⁵ M) prevented 
mitosis until 50 h, when the mitotic frequency was only 2.4% 
(Adamson, 1962; Adamson et al., 1969). After treatment with 
auxin, cytokinin and calcium chloride, the freshly cut slices 
showed mitotic frequency of 5.7%, after 37 h and 7.0% after 
50 h. However, after addition of podolactone A (2.5×10⁻⁵ M), 
the mitotic frequency was only 2.4% (Adamson, 1962; 
Adamson et al., 1969).

4.4. Insect growth inhibitory activity

Species of Podocarpus have been reported to be resistant to 
many insects and nor- and bis-norditerpenes such as nagilact-
one of these plants have been shown to be responsible. 
Norditerpene di lactones had insect-feeding-deterrent activity, 
bi flavones had growth inhibitory activity and a phytoecdysone 
had ecdysis-inhibitory activity. As part of an apparently 
atachymechanical defense mechanism, nagilactone C, D and F 
and podolide show insecticidal activity against Heliothis zeae, 
Spodoptera frugiperda and Pectinophora gossypiella (Kubo et al., 1984). Nagilactone C, D and F, isolated from P. gracilior 
caused insect-feeding-deterrent activity and an insecticidal 
activity (Kubo et al., 1984; cited in Zhang et al., 1992). Catechin 
in roots of P. nagi has growth inhibitory effects on Heliothis virescens larvae (Kubo et al., 1985; cited in Zhang et al., 1992).

Insect growth inhibitory activity against the pink bollworm 
P. gossypiella and the tobacco budworm, H. virescens was exhibited by the methanol stem bark extracts of P. nagi (Kubo 
and Ying, 1991). The insecticidal effects of six nagilactones from 
Podocarpus species on housefly (Musca domestica) was done by 
feeding the flies on a diet containing nagilactones B, D, E, 
podolide, hallactone B and 14-epi-ponalactone A. Nagilactone D 
 exhibited the most insecticidal activity with an LD₅₀ of 0.7 mg/ 
ml. Nagilactones C and D were also toxic to light-brown apple 
moth (Epiphyas postvittana) and codling moth (Laspeyresia 
ponomonella) (Singh et al., 1979).

The feeding deterrence and growth inhibition of nagilactones of 
P. nagi on the first and fifth instar larvae of the tobacco 
budworm (H. virescens) was tested. The growth of the first 
instar was strongly inhibited by nagilactone C and D in the 
artificial diet feeding assay. At 166 ppm of nagilactone D, none 
of the larvae developed to the third instar and all eventually 
died, while at 168 ppm of nagilactone C only 53.33% of the 
larvae reached the third larval instar but growth was delayed for 
six days. When the fifth instar larvae were fed with a diet 
containing nagilactone D at 160 ppm, most of the larvae could 
not pupate (growth inhibition of 65%). The few successful 
pupation events yielded small, malformed pupae and none of 
the pupae developed further. When the larvae were fed diets 
containing nagilactone D, there was potent feeding inhibition 
but when this compound was injected without contacting the 
mouth-part sensory receptors there was no effect on the food 
consumption index, indicating that different mechanisms might 
be involved in the feeding inhibition (Zhang et al., 1992).

Ponasterone A, a phytoecdysterone that inhibits ecdisis in 
sects was isolated and described from P. nakaii (Nakanishi 
et al., 1966). When this compound was tested with Samia cynthia 
and Calliphora, the activity expressed was of the same order as 
that of 20-hydroxyecdysone (inhibit the development and 
production of certain insect pests). This compound also induces 
moulting in housefly and silkworms (Kobayashi et al., 1967). An 
insect moulting hormone, crustecdysone has been isolated from 
the Australian brown pine, P. elatus (Galbraith and Horn, 1969). 
Ponasterone A, B and C from P. nakaii, P. macrophyllus and 
P. nagi contain insect moulting hormonal factor (Kobayashi et al., 
1967), which has been used in the production of high quality 
silkworm cocoons. This hormone, when administered to the 
silkworm larvae in a later stage of final instar, increased the yield 
of cocoons per unit amount of feedstuff, namely, feed efficiency, 
remarkably (Tetsuo et al., 1976). Ponasterone A can also be used 
as a biological control for pests since it greatly inhibits larval 
development in several insects (Harborne et al., 1998). One 
species, P. nakaii is a popular pest control plant in eastern 
medcine (Nakanishi, 2006).

4.5. Gastroprotective activity

The gastroprotective activity of ferruginol, a compound that 
is also found in P. ferrugineus D. Don, was assessed using 
different in vitro models. The effect of ferruginol on the healing 
of subacute gastric lesions in rats and the effect of ferruginol on 
lipoperoxidation of human erythrocyte membranes, free radical 
scavenger activity and reduced glutathione (GSH) content was 
 studied. In addition to this, prostaglandin E₂ (PGE₂) levels in 
human gastric epithelial cells (AGS), its protection against 
sodium taurocholate-induced damage, its capacity to stimulate 
the proliferation of human epithelial gastric cells and human 
 fibroblasts in culture and its cytotoxicity was investigated 
(Rodriguez et al., 2006).

Ferruginol displayed a strong gastroprotective effect at 
25 mg/kg comparable to lansoprazole at 20 mg/kg in the gastric 
lesions induced by HCL/EtOH in mice. No effect on the 
decolouration of DPPH at different concentrations of ferruginol 
was observed, neither on superoxide anion scavenging and 
GSH content. A significant inhibition of lipoperoxidation on 
erythrocyte membranes was observed with an IC₅₀ value of 
1.4 µM while the reference compound, catechin showed an IC₅₀ 
value of 260 µM, this activity contributes to the recovery of the 
 ulcerated lesion. The effect of ferruginol on the PGE₂ content of
AGS cell cultures was studied since some terpenoids act as gastroprotectives increasing the gastric prostaglandin content. At concentrations of 6 and 12 µM, ferruginol induced a strong increase on the PGE2 levels in the cell cultures. This stimulating effect on the PGE2 content was attenuated when the cells were pretreated with indomethacin. Ferruginol did not protect AGS cells against damage induced by sodium taurocholate; it proved to have strong ulcer healing activity in rats at 25 and 50 mg/kg with a curative ratio of 79.6%. Additional treatment with ferruginol at 50 mg/kg displayed a significant increase of gastric mucosal thickness similar to ranitidine (633 µM and 759 µM respectively). A stimulating effect on the cell proliferation was observed at 1 and 2 µM for AGS cells and at 4 and 8 µM for MRS-5 fibroblasts. Ferruginol showed toxicity value of 24 and 26 µM against AGS and MRC-5 cells respectively. Terpenoid carbenixolone (reference compound) showed IC50 values of 53 and 220 µM for AGS cells and MRC-5 fibroblasts, respectively. This significant stimulation indicates that ferruginol may improve the healing of wounds after gastric mucosal damage promoting the repair of the injured tissue (Rodriguez et al., 2006).

At a single oral dose of 25 mg/kg, ferruginol showed a gastroprotective activity similar to the reference drug Lansoprazole at 20 mg/kg in the model of gastric lesions induced by HCl/EtOH in mice, reducing the appearance of lesions by 60%. This activity is much more significant when compared with the majority of the reported gastroprotective diterpenes such as clerodane, labdane and abietane skeletons with significant effects at oral doses of 50 to 100 mg/kg (Schmeda-Hirschmann et al., 2002; Almeida et al., 2003; Sepulveda et al., 2005; cited in Rodriguez et al., 2006).

The gastroprotective activity exhibited by ferruginol may be one of the reasons why some species of Podocarpus s.l. are used in traditional medicine in treating stomach disorders. The berries from P. totara are used to treat constipation in women. Fruits of P. nagi are used as carminative, pectoral and stomachic and seeds are used to treat stomach diseases. The bark of P. macrophyllus is used as a tonic for stomach complaints and the Maasai use the bark of P. latifolius for stomach aches.

4.6. Other activities

Hypocholesterolemic activity of totarol was studied on four-week-old Wistar rats. A reduction in the elevation of serum cholesterol levels induced by cholesterol feeding of 27% was observed for the 0.1% totarol fed rats. At 0.3% of totarol fed rats, serum cholesterol was reduced by 52% relative to controls and cholesterol absorption was reduced by 25% (Enamoto et al., 1977). Clarkson et al. (2003), reported antiproliferative activity for totarol against a chloroquine-resistant strain of Plasmodium falciparum at an IC50 of 4.29 µM, which was 40-fold less than its cytotoxic activity against CHO cells. Totarol displayed larvicidal activity against mosquito larvae (LC50 0.25–0.37 µg/ml) (Lee et al., 2000).

A number of natural biflavonoids isolated from P. macrophyllus have exhibited anti-inflammatory activity through regulation of pro-inflammatory gene expression in vitro and in vivo. These molecules also exhibit phospholipase A2 and cyclooxygenase-2 inhibitory activity (Kim et al., 2008). TotarolTM, obtained from dried timber P. totara using patent supercritical fluid extraction process is effective as a topical anti-inflammatory agent (Gendemeno, 2005). TotarolTM (0.3% w/v and 0.1% w/v) compared with hydrocortisone, reduced the anti-inflammatory response induced by oxazolone in a dose-dependent manner. Oils from the seeds of P. nagi inhibited arachidonic acid-induced oedema in mice (Berger and Jomard, 2001). A number of Podocarpus s.l. has been used traditionally in treating inflammatory related disorders. For example, a decoction from the leaves of P. nerifolius is used for treating rheumatism and painful joints, powder from the bark of P. falcatus is used for curing headaches and a number of species are used for stomach aches.

Six diterpenoids isolated from P. nagi; totarol, totaradiol, 19-hydroxytotarol, totarol, 4-beta-carboxy-19-nortotarol and sugiol exhibited antioxidant activity by inhibiting microsomal lipid peroxidation induced by Fe (III)-ADP/NADPH and mitochondrial lipid peroxidation induced by Fe (III)-ADP/ NADH. Totarol inhibited linoleic acid autoxidation, mitochondrial and microsomal lipid peroxidation induced by Fe (III)- ADP/NADPH. Furthermore, totarol protected the red cells against oxidative hemolysis (Haraguchi et al., 1997). Totarol protected mitochondrial respiratory enzyme activities against NADPH induced oxidative injury and totarane diterpenes were effective in protecting biological systems and functions against various oxidation stress phenomena (Haraguchi et al., 1997; cited in Bernabeu et al., 2002).

Applications of natural products which inhibit tyrosinase are finding their way into the cosmetic industry. Compounds with such activities have been isolated from Podocarpus species. The effect of 2, 3-dihydro-4′, 4′-di-O-methylamentoflavone isolated from P. macrophyllus var. macrophyllus against free radical and melanin synthesis in human epidermal melanocytes (HEMn) was investigated using Western blot analysis of tyrosinase-related proteins and quantitative real time PCR. At a concentration of 100 µM, 2, 3-Dihydro-4′, 4′-di-O-methylamentoflavone showed less toxicity in HEMn cells (>80% viability). This compound showed the most potent inhibition of tyrosinase at 0.1 mM (53.2% inhibition). The inhibition was in a concentration-dependent manner ranging from 0.04 to 0.1 mM, and its IC50 was 0.098 mM compared to the positive control arbutin (IC50 3.0 mM) (Cheng et al., 2007).

Treatment using various concentrations of 2, 3-dihydro-4′, 4′-di-O-methylamentoflavone (0.04 mM, 0.05 mM, 0.06 mM and 0.1 mM) for 24 h strongly inhibited the expression of tyrosinase-related protein-2 (TRP-2) by decreasing both protein and mRNA level. This is very important when human cells are exposed to hyper-pigmentation causing agents since TRP-2 is thought to affect the cytotoxicity of melanogenic intermediates in the pigment synthetic pathway of melanocytes and also associated with resistance of human melanomas to DNA damaging drugs and radiation treatment. Hence, this compound is believed to affect cytotoxicity of melanogenic intermediates in melanocytes which may therefore reduce pigment production (Cheng et al., 2007).
Methanol leaf extracts of *P. andina* exhibited various biological activities such as plant growth regulation, insect growth inhibition, antitumor and molluscidial activities. These activities, except the molluscidial activity, were attributed to nor- and bis-norditerpene dilactones isolated from the *Podocarpus* plants. Bioassay guided isolation was used to assay for activities, except the molluscidal activity, were attributed to biological activities such as plant growth regulation, insect growth regulatory and herbivorous mammalian antifeedant activities. However, in some studies the type of inhibitory activity, the concentrations of compounds isolated from these species have shown a range of plant growth regulatory, insect growth regulatory and herbivorous mammalian antifeedant activities. However, in some cases limited availability of samples (plant material and amount of compound isolated) or the activities exhibited by these compounds are not potent enough to be considered for practical uses, results in them being discarded or ignored, yet they may be of use in terms on enhancing biological activities of known anti-infective agents. This can be possible by combining two or more substances, since it may not only be the most promising strategy for efficient utilization of renewable natural substances, but it maybe also be possible that the microorganisms may take longer to develop their resistance to two or more toxins in which the mode of action is diverse. For example, polygodial isolated from various plants increased the antifungal activity against *S. cerevisiae* and *Candida utilis* of several antibiotics such as actinomycin D and rifampicin (Kubo et al., 1976; Taniguchi et al., 1988). In this case, synergistic effects are based on the increased permeability of the plasma membrane of the antimicrobial agents when they are combined with polygodial (Taniguchi et al., 1988).

Abnormal skin or dermal hyper-pigmentation can cause significant psychological stress, thus the need to increase the development of effective and safe therapeutics to modulate skin pigmentation. In Africa, skin pigmentation and negative side effects of skin lightening products is on the rise. This is due to extensive use of skin lightening creams, especially by women. Flavonoids from African Podocarpaceae and related taxa elsewhere may find some applications in cosmetic products, since they reduce melanin biosynthesis, reducing skin pigmentation safely. Tyrosinase inhibitors may be clinically useful for the treatment of some dermatological disorders associated with melanin hyper-pigmentation and also useful in cosmetics for lightening and depigmentation after sunburn (Khan et al., 2006). It may therefore be of importance to assay and isolate same or similar compound(s) from African Podocarpaceae as additives for cosmetic products. Tyrosinase inhibitors may also play a role in the fruits and vegetable industries, since colour is a critical determinant for appearance of many food products (Zheng et al., 2008).

The ethnoveterinary contribution of these species also needs to be given special attention, since in Africa species of *Podocarpus* and *Afrocarpus* have several medicinal uses in livestock and dogs. Livestock diseases have a major negative impact in Africa because, unlike on other continents all five most important diseases occur here (Van Veen, 1997). Additionally, there is increased public concern regarding the use of conventional drugs in the animal industry mostly due to the emergence of drug resistance. In 1969, the Swann report resulted in the withdrawal of β-lactams from animal feed in the UK (Ruddock, 2000). The medicinal properties confirmed from this group of plants such as antibacterial and antifungal may play a major role is managing if not treating livestock diseases. Hence, there is a need to explore secondary metabolites from these plants especially the African Podocarpaceae as they are used in ethnoveterinary medicine.

Apart from the ethnomedical approaches to reveal the medicinal uses of these plants, chemotaxonomic and pharmacological approaches have proved to be useful, since significant biological activities and similarities in chemical composition have been found across the genus *Podocarpus* s.l.. Species from all the morphological groups (revised and old taxa) are used as sources of timber in their native areas, as do most conifers and
the majority have similar medicinal uses. For example, the African genera, *Podocarpus* and *Afrocarpus* are both used as medicine in humans, livestock and dogs. This shows that despite the morphological differences, most of the traditional uses amongst the groups still remain the same. Similar and different novel compounds have been isolated across the groups. These compounds appear to have chemotaxonomic value in Podocarpaceae. The biological activities of some of the identified compounds also support the rationale behind the medicinal uses of these species and may provide potential products for use in the development of modern pharmaceuticals, for example taxol, tolarol and its derivatives, ferruginol and the different types of nortiterpenes dilactones. With respect to *Podocarpus* and the new genera, chemotaxonomy, traditional uses and pharmacology can be applied in comparing potential candidates in drug discovery. The biological activities exhibited by the plant extracts and compounds isolated from *Podocarpus* s.l., provides a platform as to which African Podocarpaceae can be screened for various pharmacological activities in relations to several diseases. For example, antiplasmodial activity will play a significant role in combating malaria causing organisms, since malaria is a number one killer disease in many African countries. Other significant pharmacological activity that needs to be exploited further in the effects of these species on the central nervous system related disorders, inflammatory disorders and gastroprotective activities. Last but not least this review will add more value on the sustainable uses of these species, especially in areas where they are protected due to overexploitation, add to the knowledge base needed to advance the local management of disease, enable the local people to add value to the use of these species and also improve the quality of human life and resource depletion.

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References

Abdillahi, H.S., Stafford, G.I., Finnie, J.F., Van Staden, J., 2008. Antimicrobial activity of South African *Podocarpus* species. Journal of Ethnopharmacology 119, 191–194.

Adamson, D., 1962. Expansion and division in auxin-treated plant cells. Canadian Journal of Botany 40, 719–744.

Adamson, D., Low, V.H.K., Adamson, H., 1969. Transitions between different phases of growth in cells from etiolated pea stems, arthoke tubers and wheat coleoptiles. In: Wightman, F., Setterfield, G. (Eds.), Biochemical and Physiology of Plant Growth Substances. Runge Press, Ottawa, pp. 505–521.

Almeida, A.B.A., Melo, P.S., Hirum-Lima, C.A., Gracioso, J.S., Carli, L., Nunes, D.S., Haun, M., Souza-Brito, S., 2003. Antiulcerogenic effect and cytotoxic activity of semi-synthetic crotonin obtained from Croton cajucara Benth. European Journal of Pharmacology 472, 205–212.

Aquil, F., Khan, M.S.A., Owais, M., Ahmad, I., 2005. Effect of certain bioactive plant extracts on clinical isolates of β-lactamase producing methicillin resistant *Staphylococcus aureus*. Journal of Basic Microbiology 45, 106–114.

Arnold, T.H., Prentice, C.A., Hawkins, L.C., Snyman, E.E., Tomalin, M., Crouch, N.R., 2002. Medicinal and Magical Plants of southern Africa: An Annotated Checklist. National Botanical Institute, Pretoria. ISBN: 1-919795-62-6, pp. 112–113.

Barkera, N.P., Mullera, E.M., Mill, R.R., 2004. A yellowwood by any name: molecular systematics and the taxonomy of *Podocarpus* and the Podocarpaceae in southern Africa. South Africa Journal of Science 100, 629–632.

Becerra, J., Flores, C., Mena, J., Aquvequep, P., Alarcon, J., Bittner, M., Hernandez, H.M., Ruiz, E., Silva, M., 2002. Antifungal and antibacterial activity of diterpenes isolated from wood extractables of Chilean Podocarpaceae. Boletin de la Sociedad Chilena Quimica 47, 151–157.

Beentje, H.J., 1994. Kenya Trees, Shrubs and Lianas. National Museums of Kenya, Nairobi, Kenya, pp. 42–43.

Berger, A., Jomard, A., 2001. Fatty acid unbranched by a methylene as anti-inflammatory agents in superficial tissues of mammals. United States Societe L'Oreal S.A. http://www.freepatentsonline.com/6280755.html.

Bernaube, A., Shapiro, S., Villain, J., 2002. A MAS-NMR study of the location of -(+)-totoral, a diterpenoid bioactive molecule, in phospholipid model membranes. Chemistry and Physics of Lipids 119, 33–39.

Bishy, F.A., Roskov, Y.R., Orwell, T.M., Nicholson, D., Paglinawan, L.E., Bailly, N., Kirk, P.M., Bourgoin, T., Van Hertum, J., 2008. Species 2000 & IT IS Catalogue of Life: 2008 Annual Checklist. Digital source at www.catalougueoflife.org/annual-checklist/2008/. Species 2000: Reading, UK.

Bishy, F.A., Roskov, Y.R., Orwell, T.M., Nicholson, D., Paglinawan, L.E., Bailly, N., Kirk, P.M., Bourgoin, T., Baillargeon, G., 2009. Species 2000 & IT IS Catalogue of Life: 2009 Annual Checklist. Digital source at www.catalougueoflife.org/annual-checklist/2009/. Species 2000: Reading, UK.

Brown, K.S., Sanchez, W.E., 1974. A survey of the *Podocarpus* dilactones. Biochemical and Systematics Ecology 2, 11.

Brunniatt, R.K., Mill, R.R., Farjon, A., 2004. The significance of ‘it’ in the nomenclature of the three Tasmanian conifers: *Microcachrys tetragona* and *Microstrobos niphophilus* (Podocarpaceae) and *Diselma archeri* (Cupressaceae). Taxon 53, 529–539.

Buchholz, J.T., Gray, N.E., 1948. A taxonomic revision of *Podocarpus* I. The sections of the genus and their subdivisions with special reference to leaf anatomy. Journal of the Arnold Arboretum 29, 49–63.

Cheng, K.T., Hsu, F.L., Chen, S.H., Hsieh, P.K., Huang, H.S., Lee, C.K., Lee, M.H., 2007. New constituent from *Podocarpus macrophyllus* var. *macrophyllus* shows anti-tyrosinase effect and regulates tyrosinase-related proteins and mRNA in human epidermal melanocytes. Chemical and Pharmaceutical Bulletin 55, 757–761.

Chopra, R.N., Nayar, S.L., Chopra, I.C., 1986. Glossary of Indian Medicinal Plants (including the supplement). Council of Scientific and Industrial Research, New Delhi, India.

Clarke, D.B., Weavers, R.T., Perry, N.B., 2003. Intraspecific variation of foliage terpenes of *Podocarpus hallii*. Journal of Essential Oil Research 15, 234–237.

Clarkson, C., Musonda, C.C., Chibale, K., Campbell, W.E., Smith, P., 2003. Synthesis of tofarol amino alcohol derivatives and their antiplasmodial activity and cytotoxicity. Bioorganic and Medical Chemistry 11, 4417–4422.

Conran, J.G., Woods, G.M., Martin, P.G., Dowd, J.M., Quinn, C.J., Gadek, P.A., Price, R.A., 2000. Generic relationships within and between the gymnosperms families Podocarpaceae and Phyllocladaceae based on an analysis of chloroplast gene *rbcL*. South African Journal of Science 100, 629–632.

Crowe, A., 1990. A Native Edible Plants of New Zealand. Hodder and Stoughton. ISBN: 0-340-508302.

Cunningham, A.B., 1993. Ethics, Biodiversity, and New Natural Products Development. WWF International Publications Unit.
Usher, G., 1974. A Dictionary of Plants Used by Man. Constable Press, London.
Van der Merwe, I., 1998. The Knysna and Tsitsikamma Forests: Their History, Ecology and Management. Department of Water Affairs and Forestry, Knysna, South Africa.
Van Veen, T.W.S., 1997. Sense or nonsense? Traditional methods of animal parasitic disease control. Veterinary Parasitology 71, 177–194.
Venter, F., Venter, J.A., 1996. Making the Most of Indigenous Trees. Briza Publications, South Africa, p. 158. ISBN: 1-875093-05-2.
Vie, J.C., Hilton-Taylor, C., Pollock, C., Ragle, J., Smart, J., Stuart, S.N., Tong, R., 2006. The IUCN Red List: A Key to Conservation Tool. IUCN Gland, Switzerland.
Wang, X., Cai, P., Chang, C.J., Ho, D.K., Cassady, J.M., 1997. Three new cytotoxic norditerpenoids dilactones from *Podocarpus purdieanus* Hook. Natural Product Research 10, 59–67.
Watt, J.M., Breyer-Brandwijk, M.G., 1962. The Medicinal Plants and Poisonous Plants of Southern and Eastern Africa, 2nd ed. Livingstone, London.
Weiner, M.A., 1980. Earth Medicine, Earth Food. Ballantine Books 0-449-90589-6.
Wiersema, J.H., León, B., 1999. World Economic Plants: A Standard Reference. CRC Press. ISBN: 0-532-42154-5.
Xuan, L.J., Xu, Y.M., Fang, S.D., 1995. Three diterpene dilactone glycosides from *Podocarpus nagi*. Phytochemistry 39, 1143–1145.
Zhang, M., Ying, B.P., Kubo, I., 1992. Nagilactone C from *Podocarpus nagi* and their effects on the feeding and growth of tobacco budworm. Journal of Natural Products 55, 1057–1062.
Zheng, Z.P., Cheng, K.W., Chao, J., Wu, J., Wang, M., 2008. Tyrosinase inhibitors from paper mulberry (*Broussonetia papyrifera*). Food Chemistry 106, 529–535.