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 latissimo* (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 Podocarpa-ceae 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 *rbc*L sequences retrieved three main clades (Podocarpoid, Dacrydioid 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 ethnopharmacological 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 ethnobotanical 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 dacrydioides* 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 m^3 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.) Kuntze; *Nageia falcata* var. *gaussenii* (Woltz) Silba; *Podocarpus falcatus* (Thunb.) Endl.; *Podocarpus gaussenii* Woltz; *Podocarpus gracillimus* 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	*Nageia mannii* (Hook.) Kuntze Var. *usambarensis (Pilg.) Silb.*; *Nageia mannii* var. *usambarensis* (Pilg.) Silba; *Podocarpus usambarensis* Pilg.	Burundi, Kenya, Rwanda, Tanzania, Zaire	(Farjon, 1998; tIPNI, 2008)
Amentotaxus argotaenia (Hance) Pilg.	*Cephalotaxus argotaenia* (Hance) Pilg.; *Nageia argotaenia* (Hance) Kuntze; *Podocarpus argotaenia* Hance	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 dacrydioides (A. Rich.) de Laub.	*Dacrydium excelsum* D. Don; *Nageia dacydiodes* (A.Rich.) F. Muell.; *Nageia excels* (D. Don) Kuntze; *Podocarpus dacrydioides* 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. *palutus* de Laub.; *Dacrycarpus imbricatus* var. *robustus* 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) Kuntze	*Podocarpus wallichianus* C. Presl	China, India, Indonesia, Malaysia, Papua New Guinea, Philippines, Thailand	(ePIC, 2009; GRIN, 2009)
Nageia nagi (Thunb.) Kuntze	*Agathis veitchii* (Henkel & W. Hochst.) Seward & Ford; *Dammara veitchii* Henkel & W. Hochst.; *Decussocarpus nagi* (Thunb.) Laub.; *Decussocarpus nagi* var. *formosensis* (Dummer) Silba; *Myrica nagi* Thunb.; *Nageia caesia* (Maxim.) Kuntze; *Nageia cuspidata* (Endl.) Gordon; *Nageia formosensis* (Dummer) C. N. Page; *Nageia grandifolia* (Endl.) Gordon; *Nageia nagi* var. *formosensis* (Dummer) Silba; *Nageia nagi* var. *koshuensis* (Kaneh.) D. Z. Fu; *Nageia nankoensis* (Hayata) R. R. Mill; *Nageia ovata* Gordon; *Podocarpus caesius* Maxim.; *Podocarpus cuspidatus* Endl.; *Podocarpus formosensis* Dummer; *Podocarpus formosensis* var. *koshuensis* (Kaneh.) Merr. & Yamam.; *Podocarpus grandifolius* Endl.; *Podocarpus japonicus* J. Nelson; *Podocarpus koshunensis* (Kaneh.) Kaneh.; *Podocarpus nageia* R. Br. ex Endl.; *Podocarpus nagi* (Thunb.) Pilg.; *Podocarpus nagi* var. *caesius* (Maxim.) Makino; *Podocarpus nagi* (Thunb.) Makino, *Podocarpus nagi*	China, Japan, Taiwan	(Facciola, 1990; Huxley, 1992; GRIN, 2009)

	(Thunb.) Zoll. & Moritz.; *Podocarpus nagi* var. *koshunensis* Kaneh.; *Podocarpus nagi* var. *ovatus* (Gordon) Makino; *Podocarpus nankoensis* Hayata; *Podocarpus ovatus* (Gordon) Henkel & W. Hochst.		
Phyllocladus aspleniifolius (Labill.) Hook. f.	*Phyllocladus rhomboidalis* Rich; *Podocarpus aspleniifolius* (Labill.) Hook. f.	Tasmania	GRIN (2009)
Podocarpus alpinus R. Br. ex Hook. f.		Australia; New South Wales, Victoria and Tasmania	(Huxley, 1992; GRIN, 2009)
Podocarpus capuronii de Laub.		Madagascar	(Bisby et al., 2008; GBIF, 2009; GRIN, 2009)
Podocarpus costalis C. Presl	*Nageia costalis* (C. Presl) Kuntze; *Podocarpus costalis* var. *taiwanensis* Gaussen	Philippines, Taiwan	Bisby et al. (2008)
Podocarpus cunninghamii Colenso	*Nageia hallii* (Kirk) Kuntze; *Podocarpus hallii* Kirk; *Podocarpus totara* var. *hallii* (Kirk) Pilg.	New Zealand	(GBIF, 2009; GRIN, 2009)
Podocarpus elatus R. Br. ex Endl.	*Margbensonia elata* (R. Br. ex Endl.) A. V. Bobrov & Melikyan; *Nageia elata* (R. Br. ex Endl.) F. Muell.	Australia	(Facciola, 1990; Huxley, 1992; Bisby et al., 2008; GRIN, 2009)
Podocarpus elongatus (Aiton) L'Hér. ex Pers.	*Nageia elongata* (Aiton) F. Muell.; *Podocarpus thunbergii* var. *Angustifolia*; *Taxus capensis* Lam.; *Taxus elongata* Aiton	South Africa	(Palgrave, 2002; ePIC, 2009; Bisby et al., 2008; GRIN, 2009)
Podocarpus fasciculus de Laub.	*Podocarpus macrophyllus* (Thunb.) Sweet var. *liukiuensis* Warb.; *Podocarpus macrophyllus* Sweet f. *grandifolia* Pilg.	Japan, Taiwan	Farjon (1998)
Podocarpus glomeratus	*Nageia glomerata* (D. Don) Kuntze; *Podocarpus cardenasii* J. Buchholz & N. E. Gray; *Podocarpus rigidus* Klotzsch ex Endl.	Ecuador, Bolivia, Peru	(Bisby et al., 2008; GRIN, 2009)
Podocarpus gnidioides Carrière		Australia, Costa Rica, India, Malaysia, Philippines, New Caledonia, New Britain, New Zealand, South America	Silba, 1986; NCBI Taxonomy
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	Belize, Colombia, Costa, Rica, Ecuador, Guatemala, Honduras; Nicaragua, Panama	(Farjon, 1998; GRIN, 2009)
Podocarpus humbertii		Madagascar	
Podocarpus henkelii Stapf ex Dallim. & A. B. Jacks	*Podocarpus ensiculus* Melville	South Africa, Tanzania	(Palgrave, 2002; Bisby et al., 2008; GRIN, 2009)
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.; *Thuja javanica* Burm. f.	Fiji, Thailand	Bisby et al. (2009)
Podocarpus lambertii Klotzsch ex Endl.		Argentina, Brazil	GRIN (2009)
Podocarpus latifolius (Thunb.) R. Br. ex Mirb.	*Podocarpus milanjianus* Rendle; *Podocarpus thunbergii* Hook.; *Taxus latifolia* Thunb.	Angola, Cameroon, Kenya, Malawi, Mozambique, Nigeria, South Africa, Sudan, Swaziland, Uganda, Zaire, Zambia, Zimbabwe	(Palgrave, 2002; GRIN, 2009)
Podocarpus lawrencei Hook. f.	*Podocarpus alpinus* R. Br. ex Hook. f.; *Podocarpus alpinus* R. Br. ex Mirbel; *Podocarpus acutifolius* Kirk; *Podocarpus alpinus* var. *lawrencei* (Hook. f.) Hook. f.	Australian: Tasmania, Victoria and New South Wales	(Silba, 1986; Harden, 1996; GRIN, 2009)
Podocarpus macrophyllus (Thunb.) Sweet	*Taxus macrophylla* Thunb.	Japan, Taiwan	(ePIC, 2009; GRIN, 2009)
Podocarpus madagascariensis de Laub.		Madagascar	GRIN (2009)

Table 1 (*continued*)

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 leptostachya* (Blume) Kuntze; *Nageia neglecta* (Blume) Kuntze; *Nageia neriifolia* (D. Don) Kuntze; *Podocarpus decipiens* N. E. Gray; *Podocarpus discolor* Blume; *Podocarpus endlicherianus* Carrière; *Podocarpus junghuhnianus* Miq.; *Podocarpus leptostachyus* Blume; *Podocarpus macrophyllus* var. *acuminatissima* E. Pritz.; *Podocarpus neglectus* Blume; *Podocarpus neriifolius* var. *decipiens* (N. E. Gray) Silba; *Podocarpus neriifolius* var. *linearis* Wasscher; *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 macrostachyus* Parl.; *Podocarpus monteverdeensis* de Laub.; *Podocarpus oleifolius* var. *costaricensis* J. Buchholz & N. E. Gray; *Podocarpus oleifolius* var. *equadorensis* Silba; *Podocarpus oleifolius* var. *macrostachyus* (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		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. 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)

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	Farjon et al. (1993)
Podocarpus spruce		Ecuador, Peru	Bisby et al. (2008)
Podocarpus tepuiensis J. Buchholz & N. E. Gray		Venezuela	Bisby et al. (2008)
Podocarpus totara G. Benn. Ex D. Don	*Nageia totara* (D. Don) Kuntze; *Podocarpus hallii* (T. Kirk.); *Podocarpus totara* var. *waihoensis*	New Zealand	(GBIF, 2009; GRIN, 2009)
Podocarpus transiens		Brazil	Bisby et al. (2008)
Prumnopitys amara (Blume) de Laub.	*Podocarpus amarus* Blume		Bisby et al. (2008)
Prumnopitys andina (Poepp. Ex Endl.) de Laub.	*Podocarpus andinus* Poepp. ex Endl.; *Podocarpus spicatus* Poepp.		GRIN (2009)
Prumnopitys ferruginea (D. Don) de Laub.	*Nageia ferruginea* (G. Benn. ex D. Don) F. Muell.; *Podocarpus ferrugineus* D. Don; *Stachycarpus ferrugineus* (G. Benn ex D. Don) Tiegh.	New Zealand	(Bisby et al., 2008; GRIN Taxonomy of Plants, 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.	*Podocarpus ladei* F.M. Bailey	Australia	Bisby et al. (2008)
Prumnopitys montana (Humb. & Bonpl. ex Willd.) de Laub.	*Taxus montana, Podocarpus taxifolia* H.B.K.	Colombia, Ecuador, Peru, Venezuela	Silba (1986)
Prumnopitys taxifolia (Sol. ex D. Don) de Laub.	*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.	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 dulcamarus* Seem.; *Podocarpus eurhynchus* 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 elatus R. Br. Ex Endliener	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 elongatus L' Hèrit.	South Africa	The light-brown, soft durable, moderately strong, elastic, resinous, pale yellow brown wood is used for building houses, railway sleepers, beams, planks, rafters and furniture.	(Uphof, 1968; Usher, 1974)
Podocarpus falcatus (Thunb.) R. Br. Ex Mirb.	South Africa, East 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.	
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; Facciola, 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 nivalis	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; Facciola, 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. The bark is used for tanning.	(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	This 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 neriifolius 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 (tũtaki) 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 Malaya 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. neriifolius* 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. falcatus* oils are said to have medicinal properties in curing gonorrhoea 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 dinorditerpenoid 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

genus (Ito and Kodama, 1976; Roy et al., 1987). *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 suggested that the occurrence pattern of major compound types clearly showed correlation with the newer taxonomy. The major flavonoids were C-glycosylflavones, flavonol 3-*O*-glycosides, flavonol 3-methlyether glycosides and dihydroflavonol glycosides (Markham et al., 1985). Totarol diterpenes and sempervirol-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, Cycadaceae 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*. Amentoflavone is an agonist of the central $GABA_A$-R benzodiazepine receptor, hence exhibiting anticonvulsant and anxiolytic activity. (−)-Epicatechin has been isolated from Hippocastanaceae, Fabaceae, Rosaceae, Podocarpaceae and Theaceae. This compound has antibacterial, anti-hyperglycaemic, anti-inflammatory, antimutagenic and antiperoxidative activities. *In vivo* studies have shown that this compound activates dopamine receptors which are involved in schizophrenia and Parkinson's
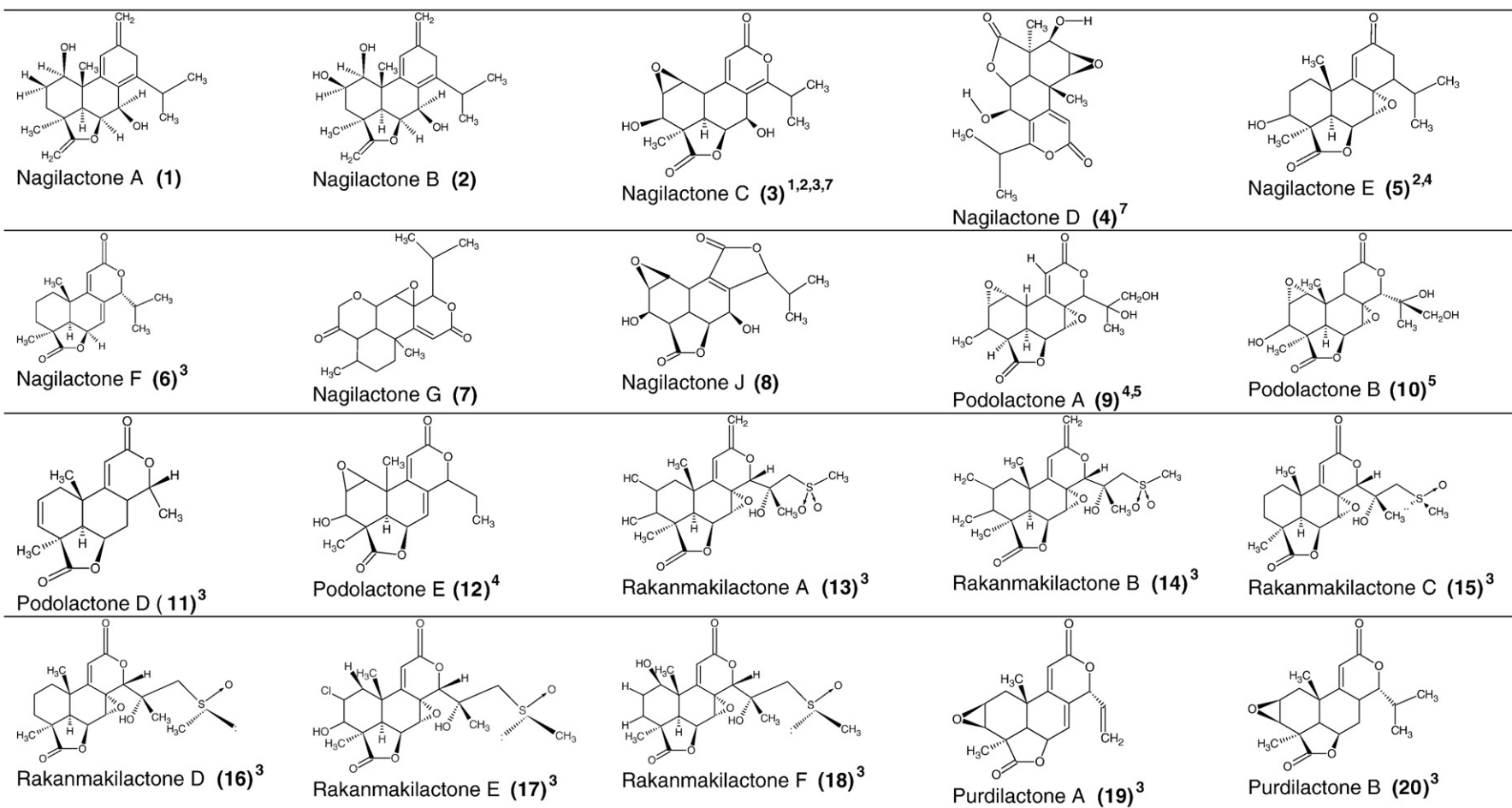
Nagilactone A **(1)**

Nagilactone B **(2)**

Nagilactone C **(3)**[1,2,3,7]

Nagilactone D **(4)**[7]

Nagilactone E **(5)**[2,4]

Nagilactone F **(6)**[3]

Nagilactone G **(7)**

Nagilactone J **(8)**

Podolactone A **(9)**[4,5]

Podolactone B **(10)**[5]

Podolactone D (**11)**[3]

Podolactone E **(12)**[4]

Rakanmakilactone A **(13)**[3]

Rakanmakilactone B **(14)**[3]

Rakanmakilactone C **(15)**[3]

Rakanmakilactone D **(16)**[3]

Rakanmakilactone E **(17)**[3]

Rakanmakilactone F **(18)**[3]

Purdilactone A **(19)**[3]

Purdilactone B **(20)**[3]

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]molluscidal; [10]larvicidal; [11]gastroprotective; [12]hypocholesterolemic; [13]anti-tyrosinase/melanin inhibition.

Purdilactone C (21)[3]

Podolide (22)[3,5]

2α-hydroxynagilactone (23)[2]

Amentoflavone (24)

Podocarpusflavone A (25)

Heveaflavone (26)

2,3-dihydro-4',4'''-di-O-methylamentoflavone (27)[13]

Totarol (28)[1,2,3,6,8,10,12]

Totaradiol (29)[1,2]

4β-carboxy-19-nortotarol (30)[1]

Totarolone (31)[1]

Inumakiol A (32)

Inumakiol B (33)[1]

Inumakiol C (34)

Inumakiol D (35)

Inumakiol E (36)

Inumakiol F (37)[1]

Inumakiol G (38)

Inumakiol H (39)[1]

Macrophyllic acid (40)[1]

Fig. 1 (continued).

Lambertic acid (41)[1]

Hinikione (42)

Hinokiol (43)

Abietatriene (44)[1,2]

Isopimarol (45)

Ferruginol (46)[1,2,3,6,11]

Acetylferruginol (47)[1,2]

Ponasterone A (48)[5]

6,7 dehydroferruginol (49)[1,2]

Podoandin (50)[4,9]

Taxol (51)[3]
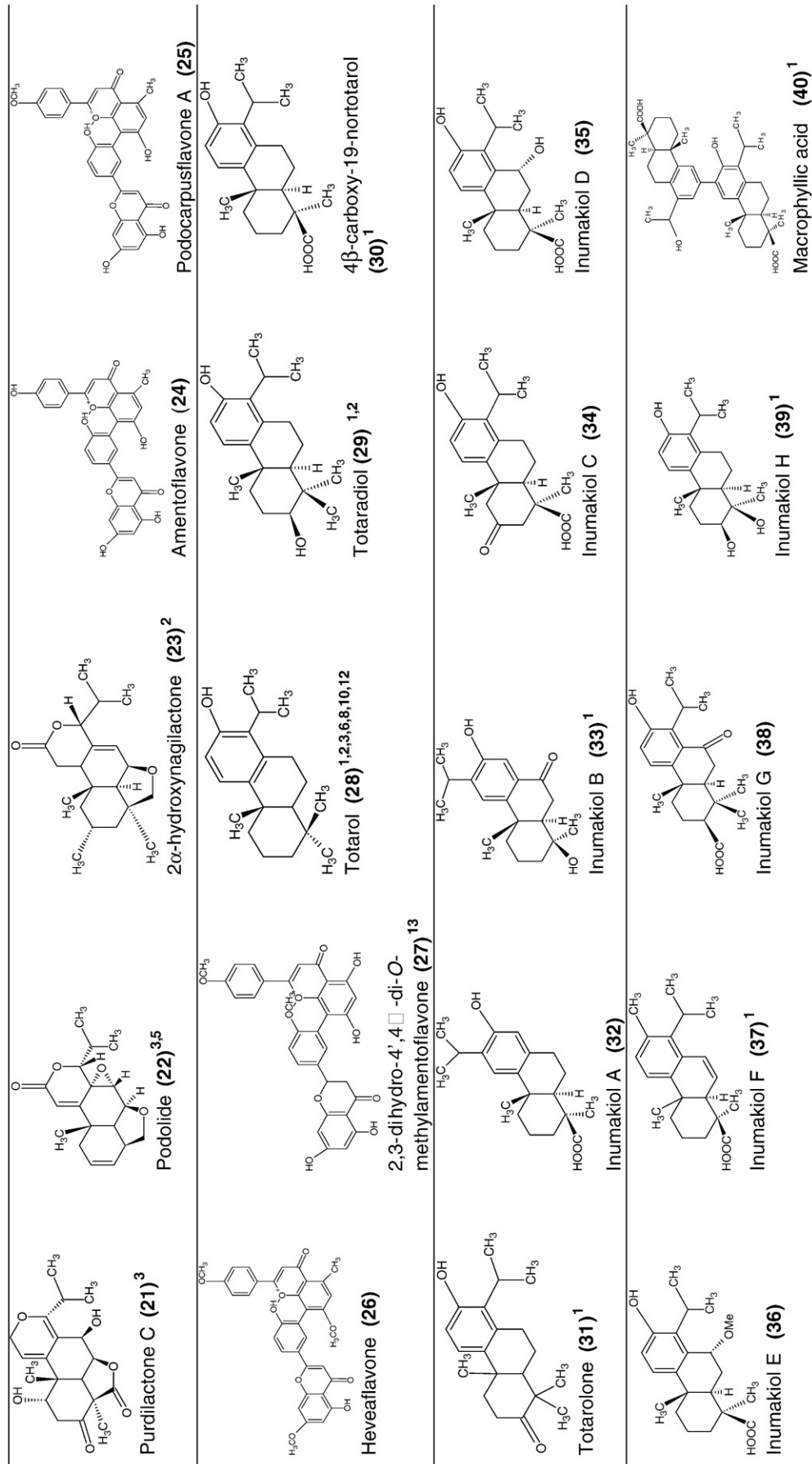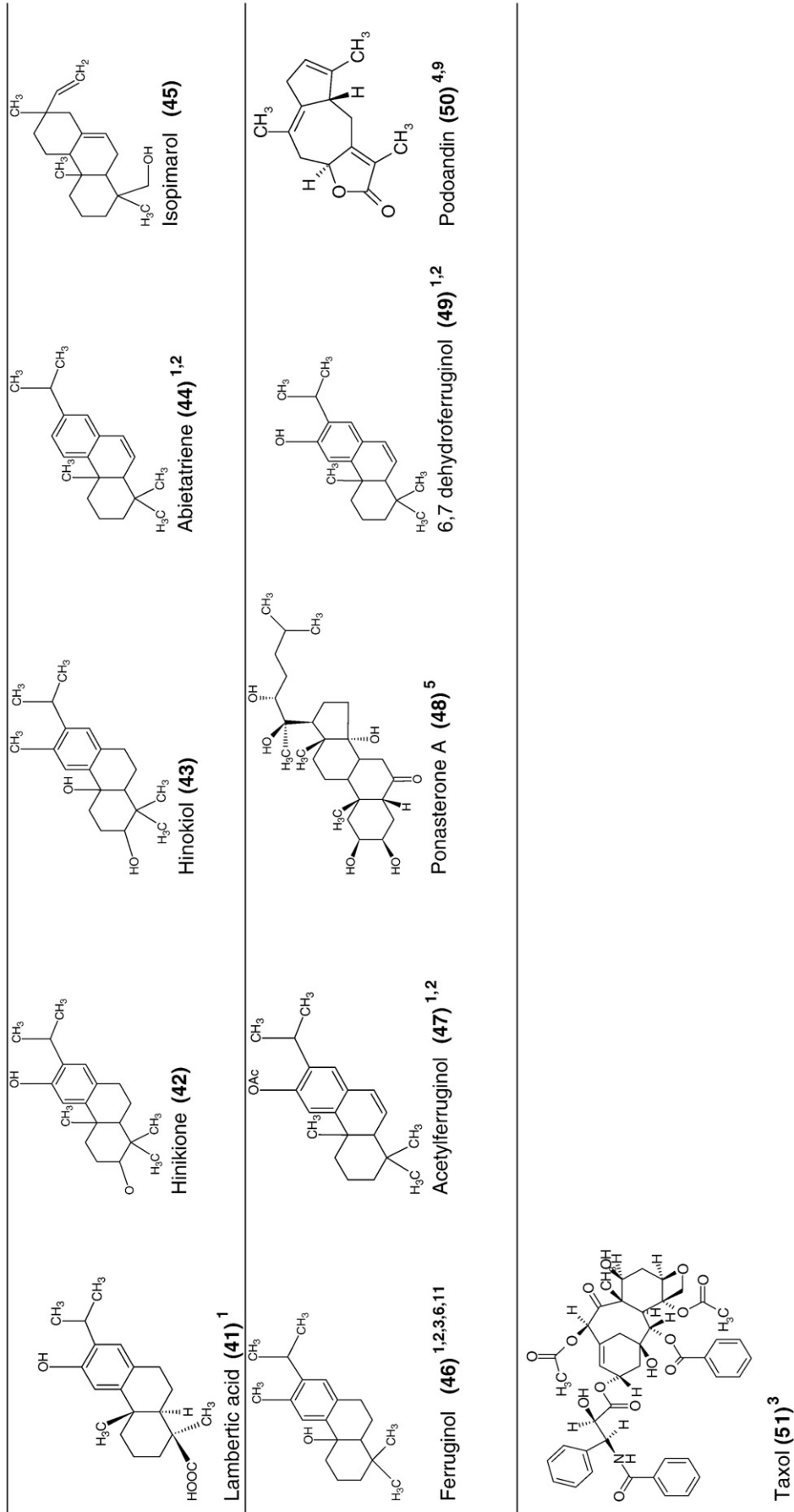
Fig. 1 (continued).

disease. It is also a prolyl endopeptidase inhibitor thus can also be used in treating Alzheimer's (Harborne et al., 1998; Polya, 2003). It might be useful to assay for such compounds in species of *Podocarpus* s.l. especially for central nervous system related disorders.

The chemical composition of essential oils of a number of *Podocarpus* s.l. species and related genera occurring in Australia and New Zealand have been analysed using GC and GC/MS. Mainly sesquiterpene and diterpene oils were identified. The sesquiterpenes include α-elemene, β-caryophyllene, α-humulene and the diterpenes include rimuene, isokaurene, phyllocladene, isophyllocladene and laurene (Clarke et al., 2003). Some of the compounds and their derivatives identified from the oils of these *Podocarpus* s.l. species have pharmacological properties. For example caryophyllene and its isomers have antibacterial, antifungal and anticancer activities (Dorman and Deans, 2000; Legault et al., 2003; Sabulal et al., 2006; Legault and Pichette, 2007). Relatively few *Podocarpus* s.l. species have been investigated for their oil content and medicinal properties, it would be of value to extract and evaluate the oils of these species in terms of type of oils (essential or carrier) and their pharmacological properties. The seeds/fruits of most of these species have lots of oil which may be used as carrier oil in diluting essential oils and absolutes used in massage, aromatherapy and cosmetics.

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 totarols 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. neriifolius* has potent antiproliferative activity against human fibrosarcoma and murine colon carcinoma tumour cell lines exhibiting ED_{50} 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. $ED_{50} \leq 4$ µg/ml (Geran et al., 1972). In another experiment the cytotoxic activity of nagilac-

tone C was more potent against human fibrosarcoma cells than the positive control 5-fluorouracil ($ED_{50} = 8.0$ 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 ED_{50} 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)-podocarpa-triene-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 IC_{50} 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 S_R-Podolactone D giving an IC_{50} value of 0.52 µg/ml and S_S-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 kaempferol 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 methicillin 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 meihei*, *Nematospora coryli*, *Penicillium notatum* and *Paecilomyces variotii* (Becerra et al., 2002). These diterpenes include ferrunigol, hinikiol, hinokione, totarol, totaradiol, totarolone, abietatriene, 6, 7 dehydroferruginol, isopimarol and acetylferruginol. 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 *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 *C. albicans*, *S. cerevisiae* and *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, macrophyllic acid, 4β-carboxy-19-nortotarol and lambertic acid isolated from *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, macrophyllic acid, a totarane diterpene dimer was the most active. The test microorganisms were *S. mutans*, *Streptococcus sobrinus*, *S. pyogenes* and *S. aureus* (aerobic bacteria), *Actinomyces viscosus*, *Porphymonas gingivalis*, *Fusobacterium nucleatum* and *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 *Actinomyces viscosus*, *P. gingivalis* and *A. actinomycetemcomitans* and for 72 h under anaerobic conditions for *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 *Podocarpus* species viz; *P. elongatus*, *P. falcatus*, *P. henkelii* and *P. latifolius* exhibited broad spectrum antimicrobial activity against *B. subtilis* (98 μg/ml), *S. aureus* (98 μg/ml), *E. coli* (390 μg/ml), *Klebsiella pneumoniae* (330 μg/ml) and *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 *B. subtilis*, and 0.26 μg/ml against the other three bacteria (Abdillahi et al., 2008).

These antimicrobial activities provides rational for the traditional uses of some of the species in treating microbial infections such as the use of oils from *P. falcatus* in treating gonorrhoea, sap from *P. falcatus*, *P. henkelii* and *P. latifolius* as a remedy for chest infections (Hutchings et al., 1996; Pankhurst, 2000). The use of the shavings from the bark of *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 *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 *Podocarpus* s.l. (Macías et al., 2000). Podolactone A significantly decreased the number of mature spikelets of *Lolium temulentum* at a lower concentration than abscisic acid (Sasse et al., 1981). This compound also counteracted the promotive effects of gibberellic 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 gibberellic 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 fusicoccin 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 gibberellic acid-induced α-amylase formation in barley embryos (Miller et al., 1984; Macías et al., 2000).

Inumakilactone B and podolactone E from *P. neriifolius* 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 6×10^{-7} M and 10×10^{-7} M respectively (Galbraith et al., 1972). Nagilactone E, from *P. nagi* was able to stimulate the growth of cultured cells of *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 *P. andina* (Poepp. & Endl.) de Laub., completely inhibited the germination of lettuce (*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 [= $100 \pm 11\%$ (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 nagilactones from these plants have been shown to be responsible. Norditerpene dilactones had insect-feeding-deterrent activity, biflavones had growth inhibitory activity and a phytoecdysone had ecdysis-inhibitory activity. As part of an apparently multichemical defense mechanism, nagilactone C, D and F and podolide show insecticidal activity against *Heliothus zea*, *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 *Heluothis 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 LD_{50} of 0.7 mg/ml. Nagilactones C and D were also toxic to light-brown apple moth (*Epiphyas postvittana*) and codling moth (*Laspeyresia pomonella*) (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 ecdysis in insects 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 reproduction 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 medicine (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 E_2 (PGE_2) 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 (Rodríguez 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 IC_{50} value of 1.4 μM while the reference compound, catechin showed an IC_{50} value of 260 μM, this activity contributes to the recovery of the ulcerated lesion. The effect of ferruginol on the PGE_2 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 PGE_2 levels in the cell cultures. This stimulating effect on the PGE_2 content was attenuated when the cells were pretreated with indomethicin. 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 IC_{50} 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 (Rodríguez 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 Rodríguez 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 to 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 antiplasmodial activity for totarol against a chloroquine-resistant strain of *Plasmodium falciparum* at an IC_{50} of 4.29 μM, which was 40-fold less than its cytotoxic activity against CHO cells. Totarol displayed larvicidal activity against mosquito larvae (LC_{50} 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 A_2 and cyclooxygenase-2 inhibitory activity (Kim et al., 2008). $Totarol^{TM}$, obtained from dried timber *P. totara* using patent supercritical fluid extraction process is effective as a topical anti-inflammatory agent (Gendimenico, 2005). $Totarol^{TM}$ (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. neriifolius* 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 IC_{50} was 0.098 mM compared to the positive control arbutin (IC_{50} 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 molluscicidal activities. These activities, except the molluscicidal activity, were attributed to nor- and bis-norditerpene dilactones isolated from the *Podocarpus* plants. Bioassay guided isolation was used to assay for molluscicidal activity and this activity was due to podoandin (a novel sesquiterpene lactone). It killed 100% (LD_{100}) of the aquatic snail *Biomphalaria glabratus* (Kubo et al., 1992).

5. Conclusions

It is apparent from this literature survey that the chemical constituents of some species of *Podocarpus*, including the revised taxa, have been broadly studied. These species have proven to be very valuable plants in the discovery and utilization of natural products particularly nor- and bis-diterpene dilactones. Since extensive research efforts have been carried out on only a very small proportion of the genus *Podocarpus* and the segregated genera (approximately 24%), there is potential and need to exploit the remaining species especially the ones with well established ethnobotanical uses. The majority of published studies were done on *P. nagi*, *P. macrophyllus*, *P. neriifolius* and *P. totara*. Recent *in vitro* and *in vivo* studies on extracts and compounds isolated from these species have shown a range of pharmacological activities such as antitumor, antimicrobial, plant growth regulatory, insect growth regulatory and herbivorous mammalian antifeedant activities. However, in some studies the type of inhibitory activity, the concentrations of inhibition, method used for screening and positive controls is not indicated. This suggests that there is a need for some of these to be re-evaluated using acceptable research methods. For some of the plant growth inhibitors, their detailed mode of action is not well understood. It would be beneficial to have such details in order to access the potential of these extracts or compounds as candidates for bioactive agents. There seems to be a need for *in vivo* validation of *in vitro* results, to further substantiate the effectiveness of the extracts and the compounds.

There is an increased interest in plant compounds which may inhibit the bacterial efflux pump since efflux is a common resistance mechanism employed by bacteria. An effective efflux pump inhibitor (EPI) could have significant benefits, including restoration of antibiotic sensitivity in a resistant strain and a reduction in the dose of antibiotic required, possibly reducing adverse drug effects (Smith et al., 2007). Another significant role of EPI is that when used with an antibiotic it delays the emergence of resistance to that antibiotic (Markham and Neyfakh, 1996). There are prospects of isolating and using EPIs clinically from African Podocarpaceae, since compounds from related species have shown such activities. The fact that totarol has both antibacterial and EPI activity against *S. aureus* indicates the possibility of isolating EPI lead compounds from these group of plants. These compounds and extracts have shown varied antimicrobial activities against several types of bacteria and fungi. 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 ethnobotanical approach 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, torarol and it's derivatives, ferruginol and the different types of norditerpenes 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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