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Rarefaction on natural compound extracts diversity among genus

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ABSTRACT

The aim of our study was to investigate the intrinsic diversity of genus based on chemical composition of natural extracts of *Cacalia*, *Dracocephalum*, *Jatropha*, *Saussurea* and *Senecio*. Four rarefaction approaches (richness, Shannon's entropy, Simpson's diversity, and max-entropy) were implemented as an algorithm and run 10,000 times. Our results showed similar patterns of richness in natural compounds according to genus and of Simpson's diversity index while max-entropy has a similar pattern as Shannon's entropy. The analysis of both richness in active compounds and weight of most frequent extracted compound revealed that *Dracocephalum* genus is most suitable for propagation.

1. Introduction

Plant phylogeny refers to the description of the evolutionary history of related species plant groups. Different information that is not limited to morphological characters [1,2], molecular [3] or genome-scale data [4] had their contribution to a phylogeny [5].

Plant extracts, and thus plant composition, are used as therapeutics from ancient times [6] and are sometimes seen as source of active compounds for new drugs [7,8]. Antibacterial effect of a series of medicinal plant extracts and/or oils have already been identified (*Terminallia chebula* [9], *Garcinia kola* [10], *Pterygota macrocarpa* and *Cola gigantea* [11], *Cryptolepine sanguinolenta* [12], *Quercus dilatata* L. [13], *Rhus coriaria* L. [14], *Launaea resedifolia* L. [15], etc.). Furthermore, the plants extracts are also used for their anti-inflammatory activities (mangrove plants [16], *Caesalpinia ferrea* [17]). Beside those main effects, other effects such as anti-oxidant (*Myrtus communis*, *Smilax aspera*, *Lavandula stoechas*, and *Calamintha nepeta* [18]), anticancer (*Zingiber officinale* Roscoe., *Atractylodes lancea* (Thung.) DC., *Piper chaba* Hunt. [19]), immunomodulation (triterpenoids ursolic acid and lupeol extracted from *Eucalyptus tereticornis* and *Gentiana kurroo* [20]), anti-viral (anti-herpes simplex virus type 1 activity of oxyresveratrol extracted from *Artocarpus lakoocha* [21]) had been identified.

The biological activity of plant extracts are of interest due to their specific activities such as anti-viral [22] and antibacterial [23,24], anticancer therapeutics [25], neuroprotection [26], antiliver fibrosis [27], and the list could continue. The identification of those extracts with specific biological activity is of main interest in order to integrate the knowledge and to develop new plant-derived drugs [28,29]. The analysis of biological activity of plant extracts is an interdisciplinary approach and moved from a simple observation to integrated approaches (involving analytical chemistry, synthesis, molecular biology, proteomics, chemoinformatics, bioinformatics, etc.). Huge amounts of various data regarding activity and/or action mechanisms of plant extracts are available [30–34]. Integrating these amounts of disperses data could bring knowledge of important relevance and may provide a measureless resource for future discovery of biomedical relevant compounds.

The aim of our study was to conduct a differentiation analysis using rarefaction approach among genera regarding natural richness in active compounds and to provide the expression of the diversity as function of number of plants that belong to a genus.

2. Materials and methods

The chemical composition of five genera, represented by *Cacalia* [35] (NE of Asia & America & SW and NW of China), *Dracocephalum* [36] (North and South America & Europe & Asia), *Jatropha* [37] (America & Africa (tropical and subtropical)), *Saussurea* [38] (Asia & Europe), and *Senecio* [39] (worldwide), represented the material of our research. The main characteristics of the genera included in the study are summarized in Table 1.

The names of compounds as well as the source of compounds for each investigated genus are available as supplementary materials

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Table 1
Main characteristics of investigated genera.

Genus (no. of plants[a])	Family[a]	Main activity	No. of Comp[b] (no. of Specie[b])
Cacalia (1008)	*Compositae*	Antioxidative; Antimicrobial; Antitumor; Citotoxic	109 (13)
Dracocephalum (231)	*Lamiaceae*	Antioxidant; Antihypoxic; Antimicrobial; Antitumor; Cardiovascular Protective Effect; Immunomodulatory; Trypanocidal	246 (12)
Jatropha (567)	*Euphorbiaceae*	Anticoagulant and coagulant; Antiinflammatory; Antitumor; Antibacterial; Antidiarrheal; Antiviral; Pregnancy-Terminating Effect	143 (26)
Saussurea (1054)	*Compositae*	Antioxidant; Antiinflammatory; Antitumor; Antimicrobial; Antiparastic; Antifeedant; Anti-Ulcer and Cholagogic; Hepatoprotective; Immunosuppressive; Spasmolytic; CNS Depressant	216 (22)
Senecio (6183)	*Compositae*	Antibacterial; Antifungal; Antiinflammatory; Antiulcer; Antifeedand effect; Antimitotic Effect; Cytotoxic (human hepatom cell line Huh-7); Angiotensin-Converting Enzyme Inhibitory; Activity; Insecticidal; Neurotoxic; Glutathione-Depleting	631 (186)

[a]Source: http://www.theplantlist.org [online] (accessed 29.05.12).
[b] Information extracted from the reference associated to each genus.

(r_cacalia.txt, r_dracocephalum.txt, r_jatropha.txt, r_saussurea.txt, and r_senecio.txt).

A simulation study was conducted based on chemical compounds extracted from investigated species to analyze intrinsic diversity by applying a rarefaction approach.

The Bootstrap method, introduced by Efron [40], was used in this analyzes to estimate (based on independent observation represented by the compounds obtained from plant extracts) the distributions of a series of statistics in order to assess what happen in population. The following statistics were obtained and used in this analysis: mean value of the number of chemical compounds (revealing the richness within species), biodiversity expressed through two entropies (Shannon entropy [41,42] and max-entropy [43,44]), and one diversity measure (Simpson diversity [45]).

The following algorithm was developed and applied in our analysis:

```
For n=1 to n=50 (number of plants to be extracted)
■  For q=1 to q=10,000 (repeat the experiment by 10,000 times)
   •  For i=1 to i=n (execute the experiment of repeated sampling)
      ■  plant_i = random(number of species)
      ■  obs_i = number of compounds for plant_i
   •  End for i
   •  Exp_q = the array containing distinct compounds and the number of
         plants from which were extracted (from n)
   •  dc_q = Count(Exp_q) - the number of distinct compounds
   •  For α = 0 (Hartley=log(Count)), 1 (Shannon), 2 (log(Simpson)), ∞
        (max-entropy)
      ■  hα_q = Renyi(Exp_q, α) - Renyi entropy of Exp_q
■  End for q
■  Calculate the mean and standard deviation (from 10,000 repetitions) for
   Count and Entropies
End for n
```

The algorithm was run 10,000 times in order to emulate changes in population. The rarefaction method [46] was furthermore applied to compare genetic diversity regarding the extracts on the investigated genus. The rarefaction analysis was applied to answer the following question "How many extracts could have been found in a small sample?" [47]. Rarefaction curves were used for graphical visualization of diversity based on the obtained results.

3. Results

The distribution of richness in natural active compounds according to genus was obtained based on applied methodology and is presented in Fig. 1. The minimum number of active compounds (average of the expectance, 4.10) was observed for *Senecio* when just one plant was included in analysis. As expected, the maximum number of compounds (average of the expectance, 243.35 – *Dracocephalum*) was observed when 50 plants were included in the sample.

The increase in number of active compounds varied from 0 (*Cacalia* and *Dracocephalum*) to 23 (*Dracocephalum*) with a minimum variation observed for *Senecio* (from 2 to 4).

Shannon's entropy represented the second method used to characterize diversity in our investigation. It had values from 1.1259 (*Senecio* – $n = 1$) to 5.3397 (*Dracocephalum* – $n = 50$) and its evolution as function of sample size is presented in Fig. 2.

The Shannon's entropy increase almost 2 times for $n = 2$ compared with $n = 1$ for *Jatropha*, *Saussurea* and *Senecio*, being the highest increasing observed in our study. Without any exception, the Shannon's entropy slightly increased with sample size but the increase proved not being uniform when the differences were analyzed.

The Simpson's diversity index varied from 3.0830 (*Senecio* – $n = 1$) to 179.8364 (*Dracocephalum* – $n = 50$). The evolution of Simpson's diversity index with sample size is presented in Fig. 3.

The entropy of most frequent compound (max-entropy) varied from 1.1259 (*Senecio* – $n = 1$) to 4.0842 (*Dracocephalum* – $n = 50$). The evolution of max-entropy with sample size is presented in Fig. 4.

The max-entropy results revealed that the value increased ~2 times when $n = 2$ is compared to $n = 1$ for *Jatropha*, *Saussurea* and *Senecio* genus. The max-entropy systematically increased with sample size just for *Senecio*. The rule of increase of max-entropy with sample size was broken 1 time by *Saussurea*, 2 times by *Jatropha*, 3 times by *Cacali*) and 9 times by *Dracocephalum*. The rarefaction curve for *Senecio* overlaps the *Jatropha* line for $n < 5$ when max-entropy was investigated.

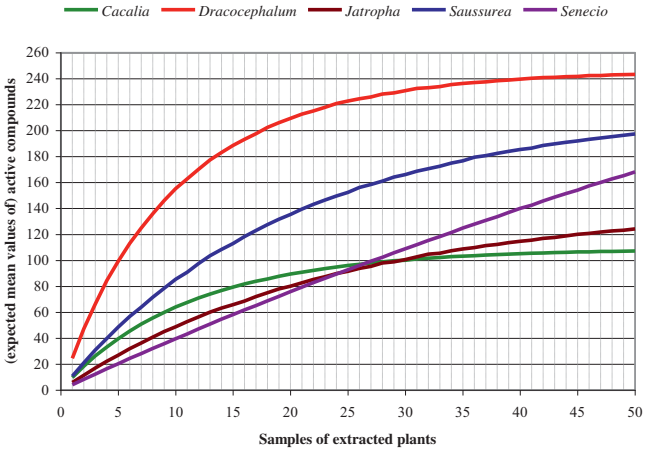

Fig. 1. Sampling active compounds richness–generic richness rarefaction curves.

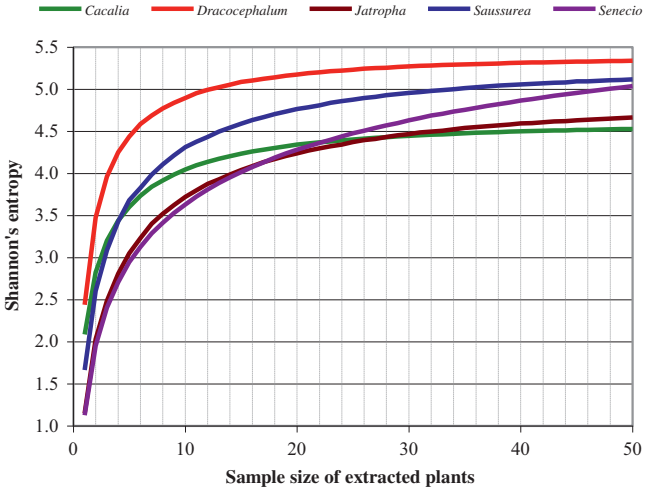

Fig. 2. Rarefaction curves of Shannon's entropy.

4. Discussion

Diversity of natural compounds extracts for *Cacalia*, *Dracocephalum*, *Jatropha*, *Saussurea*, *Senecio* genus was successfully investigated. The rarefaction approach (approach not influenced by the sample size) has been applied to compare species richness among investigated genera using shape of the curve as Sanders applied on marine species [46].

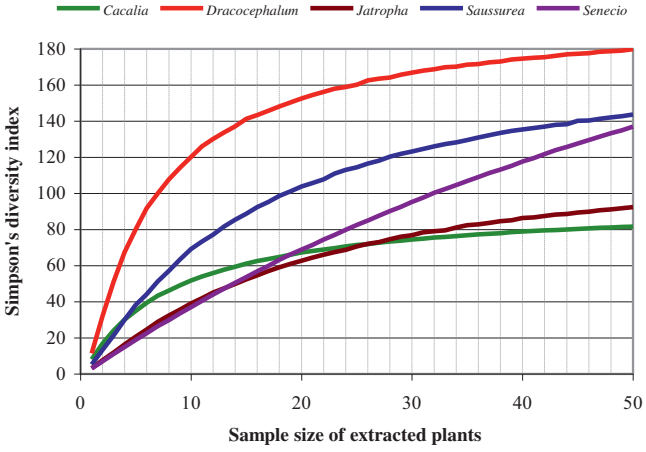

Fig. 3. Rarefaction curves of Simpson's diversity on genus.

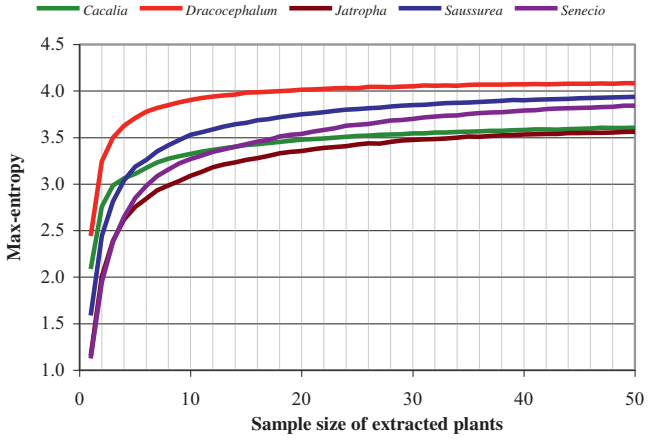

Fig. 4. Rarefaction curve max-entropy on genus.

Bioactive compounds in plants (compounds with pharmacological and toxicological effects in human and animals that are produced by plants) become of interest due to the necessity of identification of new drug with highest activity and lowest adverse effects as possible. The main groups of bioactive compounds according to biochemical pathways [48] are: glycosides (such as cardiac glycosides which are presented in plants of *Scrophulariaceae*, and *Convallariaceae* or cyanogenic glycosides that are present in species such as *Rosaceae*), flavonoids (produced by species of *Fabaceae*), tannins (species of *Fagaceae* and *Polygonaceae*), terpenoids (the most representative family is *Lamiaceae*), diterpenoids (present in *Coffea arabica*), alkaloids (such as alkaloids with acticholinergic activity present in species of *Solanaceae*), furocoumarines (in *Apiaceae* – carrot family) and naphthodianthrones, proteins and peptides (*Euphorbiaceae* or *Fabaceae*). For example, morphine (painkiller; its use lead to addiction), codeine (use to treat cough or as painkiller), noscapine (use to treat cough), and papaverine (use to treat vasospasms – heart and brain) are extracted from *Papaver somniferum* [49]. Acetyl salicylic acid used as rheumatism, painkiller, fever reducing agent, and anti-coagulant is extracted from *Salix*-species [49]. Atropine used as eye drops to study the inner parts of the eyes, and scopolamine used as travel sickness drug are extracted from *Atropa belladonna*, *Hyoscyamus niger*, and *Datura stramonium* [49].

It is estimated that only 10% of the plants on earth have been investigated for their content of bioactive compounds [49]. The investigation of at least those plants used by traditional healers could provide the faster route to new active compounds.

In this study we used four rarefaction approaches (richness, Shannon's entropy, Simpson's diversity, and max-entropy) to analyze the bioactive compounds diversity of investigated species.

The results of the first approach revealed that the richest in bioactive compounds is *Dracocephalum* (see Fig. 1). Three pathways could be observed according to genus when the differences in number of active compounds are investigated relative to the number of investigated plants (Fig. 1): first pattern that involves *Cacalia* – *Jatropha* – *Saussurea*, second pattern that comprises *Senecio* and third pattern that comprise *Dracocephalum*. As far as the first pattern is concerned, it could be observed a slightly uniform decrease of the number of active compounds regarding the difference related to previous n, with increase of number of plants included in analysis for *Cacalia* (the difference varied inverses to sample size with values from 0 to 9), *Jatropha* (the difference varied inverses to sample size with values from 1 to 5) and *Saussurea* (the difference varied inverses to sample size with values from 1 to 10). Furthermore, the difference decreased till a certain n (*Cacalia* – $n = 35$; *Jatropha* – $n = 37$, and *Saussurea* – $n = 42$) and after that became flattened (0 for *Cacalia* – $n > 35$; 1 for both *Jatropha* – $n > 37$ and

Saussurea – $n > 42$). As far as the second pattern is concerned, with one exception ($n = 41$), the difference in active compounds relative to the previous sample size was of 3 (systematically for $n > 29$) or 4 (systematically for $n < 15$). This observation could be related with the number of active compounds (this genus had the higher number of active compounds – see Table 1 – ~2.5 times higher compared to *Dracocephalum*) as well as with the richness in specie (the number of *Senecio* was more than 7 times higher compared to *Jatropha* – see Table 1) for *Senecio* genus. Regarding the third pattern, significant differences were observed till $n = 7$ (a difference of 23 compounds between $n = 2$ and $n = 1$; a difference of 12 compounds between $n = 7$ and $n = 6$) but for $n > 7$ the differences were not higher than 1 and become systematically 0 for $n > 46$. Moreover, the number of active compounds doubled when two plants were included in analysis and after this threshold the number of compounds increased slightly.

In terms of Shannon's entropy, the second approach of our study, rarefaction was identical for *Jatropha* and *Senecio* for $n < 5$ and very close till the intersection of their rarefaction curves ($n = 18$) (see Fig. 2). Starting with this point, different patterns were identified (slightly modification for *Jatropha* and increases for *Senecio*). The Shannon's entropy of *Cacalia* and *Saussurea* follow a similar pattern as of *Dracocephalum*; both showing an increase with sample size but values of Shannon entropy associated to *Dracocephalum* was higher (Fig. 2).

Simpson's diversity index, the third approach used in our investigation, follows somehow the patterns of number of compounds (Fig. 1). Thus, two pathways are observed in terms of index range: relative small ranges (*Cacalia* with a range of 73.5009 and *Jatropha* with a range of 89.1564) and relative large ranges (*Senecio* – 133.9291, *Saussurea* – 138.4330 and *Dracocephalum* – 168.3506). As it could be observed from Fig. 3, without any exception, the diversity evaluated using the Simpson's index increased with sample size. The highest increase in diversity was observed when $n = 2$ was compared to $n = 1$ (an increase of 2 times was observed for *Cacalia*, *Jatropha*, and *Senecio* and of 3 times for *Dracocephalum* and *Saussurea*). Moreover, the diversity increased twice when $n = 3$ was compared to $n = 2$ for *Dracocephalum*, *Jatropha*, *Saussurea*, and *Senecio*. For $n > 3$ the increased in diversity was uniformly of ~1. Furthermore, the smallest variation regarding the differences is observed for *Senecio* genus (Fig. 3). *Cacalia* is the genus with the difference around 0 for $n > 39$. Small variation in differences is also observed on *Jatropha* while the higher variation is observed on *Dracocephalum*.

Similar patterns with the one described for the Shannon's entropy was observed when the results of the fourth approach used in this analysis were investigated (max-entropy – Fig. 4).

The results of our study reflect the rarefaction obtained based on the information available when the research was initiated. A tendency of flattening is observed for *Cacalia* and *Dracocephalum* for both number of compounds and Simpson diversity index. Similar patterns were observed on Shannon's entropy and max-entropy as well as on Simpson diversity index and rarefaction of number of compounds. The obtained results must be interpreted taking into consideration that different species have not the same contribution to diversity [50–53]. The analysis could be extended by implementing other diversity indices such as phylogenetic diversity index [54], quadratic diversity index [55], taxanomic entropy [56], unnamed H_d index [57] or phlylogenetic entropy H_P [58] to obtain a more exhaustive investigation. Such researches are currently conducted in our laboratory to obtain more relevant results on the topic.

5. Conclusion

Our results revealed that both in terms of richness in active compounds and weight of most frequent extracted compound *Dracocephalum* genus is most suitable for propagation being followed by *Saussurea*. *Cacalia* and *Jatropha* proved to have the lowest diversity in terms of bioactive compounds related to the investigated genus.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jocs.2013.08.002.

References

[1] P. Alberch, S.J. Gould, G.F. Oster, D.B. Wake, Size and shape in ontogeny and phylogeny, Paleobiology 5 (1979) 296–317.
[2] K.C. Nixon, W.L. Crepet, D. Stevenson, E.M. Friis, A reevaluation of seed plant phylogeny, Ann. Missouri Bot. Gard. 81 (1994) 484–533.
[3] S. Mathews, Phylogenetic relationships among seed plants: persistent questions and the limits of molecular data, Am. J. Bot. 96 (2009) 228–236.
[4] J.G. Burleigh, M.S. Bansal, O. Eulenstein, S. Hartmann, A. Wehe, T.J. Vision, Genome-scale phylogenetics: inferring the plant tree of life from 18.896 gene trees, Syst. Biol. 60 (2011) 117–125.
[5] O. Gascuel, Mathematics of Evolution and Phylogeny, Oxford University Press, USA, 2005.
[6] F.A. Jones, Herbs: useful plants, J. R. Soc. Med. 89 (1996) 717–719.
[7] S.M.K. Rates, Plants as source of drugs, Toxicon 39 (2001) 603–613.
[8] D.S. Alviano, C.S. Alviano, Plant extracts: search for new alternatives to treat microbial diseases, Curr. Pharm. Biotechnol. 10 (2009) 106–121.
[9] A. Ghosh, B.K. Das, A. Roy, B. Mandal, G. Chandra, Antibacterial activity of some medicinal plant extracts, J. Nat. Med. 62 (2008) 259–262.
[10] C.T. Seanego, R.N. Ndip, Identification and antibacterial evaluation of bioactive compounds from *Garcinia kola* (Heckel) seeds, Molecules 17 (2012) 6569–6584.
[11] C. Agyare, G.A. Koffuor, V.E. Boamah, F. Adu, K.B. Mensah, L. Adu-Amoah, Antimicrobial and anti-inflammatory activities of *Pterygota macrocarpa* and *Cola gigantea* (Sterculiaceae), Evid. based complement, Altern. Med. 2012 (2012) 902394.
[12] R.C. Gopalan, E. Emerce, C.W. Wright, B. Karahalil, A.E. Karakaya, D. Anderson, Effects of the anti-malarial compound cryptolepine and its analogues in human lymphocytes and sperm in the Comet assay, Toxicol. Lett. 207 (2011) 322–325.
[13] M. Jamil, I.U. Haq, B. Mirza, M. Qayyum, Isolation of antibacterial compounds from *Quercus dilatata* L. through bioassay guided fractionation, Ann. Clin. Microbiol. Antimicrob. 11 (2012) 11.
[14] S.M. Nasar-Abbas, A.K. Halkman, Antimicrobial effect of water extract of sumac (*Rhus coriaria* L.) on the growth of some food borne bacteria including pathogens, Int. J. Food Microbiol. 97 (2004) 63–69.
[15] A. Zellagui, N. Gherraf, S. Ladjel, S. Hameurlaine, Chemical composition and antibacterial activity of the essential oils from *Launaea resedifolia* L, Org. Med. Chem. Lett. 2 (2012) 2.
[16] J.A. Shilpi, M.E. Islam, M. Billah, K.M. Islam, F. Sabrin, S.J. Uddin, L. Nahar, S.D. Sarker, Antinociceptive, anti-inflammatory, and antipyretic activity of mangrove plants: a mini review, Adv. Pharmacol. Sci. 2012 (2012) 576086.
[17] L. de, P. Pereira, R.O. da Silva, P.H. Bringel, K.E. da Silva, A.M. Assreuy, M.G. Pereira, Polysaccharide fractions of *Caesalpinia ferrea* pods: potential anti-inflammatory usage, J. Ethnopharmacol. 139 (2012) 642–648.
[18] S. Amira, M. Dade, G. Schinella, J.L. Ríos, Anti-inflammatory, anti-oxidant, and apoptotic activities of four plant species used in folk medicine in the Mediterranean basin, Pak. J. Pharm. Sci. 25 (2012) 65–72.
[19] T. Plengsuriyakarn, V. Viyanant, V. Eursitthichai, P. Picha, P. Kupradinun, A. Itharat, K. Na-Bangchang, Anticancer activities against cholangiocarcinoma, toxicity and pharmacological activities of Thai medicinal plants in animal models, BMC Complement. Altern. Med. 12 (2012) 23.
[20] A. Maurya, F. Khan, D.U. Bawankule, D.K. Yadav, S.K. Srivastava, QSAR, docking and in vivo studies for immunomodulatory activity of isolated triterpenoids from *Eucalyptus tereticornis* and *Gentiana kurroo*, Eur. J. Pharm. Sci. 47 (2012) 152–161.
[21] T. Chuanasa, J. Phromjai, V. Lipipun, K. Likhitwitayawuid, M. Suzuki, P. Pramyothin, M. Hattori, K. Shiraki, Anti-herpes simplex virus (HSV-1) activity of oxyresveratrol derived from Thai medicinal plant: mechanism of action and therapeutic efficacy on cutaneous HSV-1 infection in mice, Antiviral Res. 80 (2008) 62–70.
[22] D. Chattopadhyay, M.C. Sarkar, T. Chatterjee, D.R. Sharma, P. Bag, S. Chakraborti, M.T. Khan, Recent advancements for the evaluation of anti-viral activities of natural products, N. Biotechnol. 25 (2009) 347–368.

[23] C.L. Koh, C.K. Sam, W.F. Yin, L.Y. Tan, T. Krishnan, Y.M. Chong, K.G. Chan, Plant-derived natural products as sources of anti-quorum sensing compounds, Sensors 13 (2013) 6217–6228.
[24] M.V. Arasu, V. Duraipandiyan, S. Ignacimuthu, Antibacterial and antifungal activities of polyketide metabolite from marine *Streptomyces* sp. AP-123 and its cytotoxic effect, Chemosphere 90 (2013) 479–487.
[25] Y. Feng, N. Wang, M. Zhu, Y. Feng, H. Li, S. Tsao, Recent progress on anticancer candidates in patents of herbal medicinal products, Recent Pat. Food Nutr. Agric. 3 (2011) 30–48.
[26] M.D. da Rocha, F.P. Viegas, H.C. Campos, P.C. Nicastro, P.C. Fossaluzza, C.A. Fraga, et al., The role of natural products in the discovery of new drug candidates for the treatment of neurodegenerative disorders II: Alzheimer's disease, CNS Neurol. Disord. Drug Targets 10 (2011) 251–270.
[27] X.B. Wang, Y. Feng, N. Wang, F. Cheung, C.W. Wong, Recent progress on anti-liver fibrosis candidates in patents of herbal medicinal products, Recent Pat. Food Nutr. Agric. 4 (2012) 91–106.
[28] G.M. Rishton, Natural products as a robust source of new drugs and drug leads: past successes and present day issues, Am. J. Cardiol. 101 (2008) 43D–49D.
[29] M.C. Recio, I. Andújar, J.L. Ríos, Anti-inflammatory agents from plants: progress and potential, Curr. Med. Chem. 19 (2012) 2088–2103.
[30] H. Azimi, A.-A. Khakshur, I. Aghdasi, M. Fallah-Tafti, M. Abdollahi, A review of animal and human studies for management of benign prostatic hyperplasia with natural products: Perspective of new pharmacological agents, Inflamm. Allergy Drug Targets 11 (2012) 207–221.
[31] H.-Y. Hung, K. Qian, S.L. Morris-Natschke, C.-S. Hsu, K.-H. Lee, Recent discovery of plant-derived anti-diabetic natural products, Nat. Prod. Rep. 29 (2012) 580–606.
[32] M.A. Randhawa, M.S. Alghamdi, Anticancer activity of *Nigella sativa* (black seed) – a review, Am. J. Chin. Med. 39 (2011) 1075–1091.
[33] I. Kostova, S. Bhatia, P. Grigorov, S. Balkansky, V.S. Parmar, A.K. Prasad, L. Saso, Coumarins as antioxidants, Curr. Med. Chem. 18 (2011) 3929–3951.
[34] T.-Y. Wu, C.-P. Chen, T.-R. Jinn, Traditional Chinese medicines and Alzheimer's disease, Taiwan J. Obstet. Gynecol. 50 (2011) 131–135.
[35] M.-L. Zhanga, J.-J. Zhang, C.-H. Huoa, Y.-C. Guc, Q.-W. Shi, Chemical constituents of plants from the genus *Cacalia*, Chem. Biodivers. 7 (2010) 105–115.
[36] Q. Zenga, H.-Z. Jin, J.-J. Qina, J.-J. Fua, X.-J. Hua, J.-H. Liu, L. Yana, M. Chen, W.-D. Zhang, Chemical constituents of plants from the genus *Dracocephalum*, Chem. Biodivers. 7 (2010) 1911–1929.
[37] X.-P. Zhang, M.-L. Zhang, X.-H. Su, C.-H. Huo, Y.-C. Gu, Q.-W. Shi, Chemical constituents of the plants from genus *Jatropha*, Chem. Biodivers. 7 (2010) 2166–2183.
[38] Y.-F. Wang, Z.-Y. Ni, M. Dong, B. Cong, Q.-W. Shi, Y.-C. Gu, H. Kiyota, Secondary metabolites of plants from the Genus *Saussurea*: chemistry and biological activity, Chem. Biodivers. 7 (2010) 2623–2659.
[39] Y. Yang, L. Zhao, Y.-F. Wang, M.-L. Chang, C.-H. Huo, Y.-C. Gu, Q.-W. Shi, H. Kiyota, Chemical and pharmacological research on plants from the genus *Senecio*, Chem. Biodivers. 8 (2011) 13–72.
[40] B. Efron, Bootstrap methods: another look at the Jackknife, Ann. Statist. 7 (1979) 1–26.
[41] C.E. Shannon, A mathematical theory of communication, Bell. Syst. Techn. J. 27 (1948) 379–423.
[42] C.E. Shannon, A mathematical theory of communication, Bell. Syst. Techn. J. 27 (1948) 623–656.
[43] E.T. Jaynes, Information theory and statistical mechanics, Phys. Rev. Ser. II 106 (1957) 620–630.
[44] E.T. Jaynes, Information theory and statistical mechanics II, Phys. Rev. Ser. II 108 (1957) 171–190.
[45] E.H. Simpson, Measurement of diversity, Nature 163 (1949) 688.
[46] H. Sanders, Marine benthic diversity: a comparative study, Am. Nat. 102 (1968) 243–283.
[47] S.H. Hurlbert, The nonconcept of species diversity: a critique and alternative parameters, Ecology 52 (1971) 577–586.
[48] A. Bernhoft, A brief review on bioactive compounds in plants, in: A. Bernhoft (Ed.), Bioactive Compounds in Plants – Benefits and Risks for Man and Animals. The Norwegian Academy of Science and Letters, Proceedings from a symposium held at The Norwegian Academy of Science and Letters, Oslo, 13–14 November 2008, 2010, pp. 11–17.
[49] B.S. Paulsen, Highlights through the history of plant medicine, in: A. Bernhoft (Ed.), Bioactive Compounds in Plants – Benefits and Risks for Man and Animals. The Norwegian Academy of Science and Letters, Proceedings from a symposium held at The Norwegian Academy of Science and Letters, Oslo, 13–14 November 2008, 2010, pp. 18–29.
[50] P. Ehrlich, The loss of diversity: causes and consequences, in: E. Wilson (Ed.), Biodiversity, National Academy Press, Washington, DC, 1988, pp. 21–27.
[51] R. May, Taxonomy as destiny, Nature 347 (1990) 129–130.
[52] C. Humphries, P. Williams, R. Vane-Wright, Measuring biodiversity value for conservation, Annu. Rev. Ecol. Syst. 26 (1995) 93–111.
[53] R. Crozier, Preserving the information content of species: genetic diversity, phylogeny, and conservation worth, Ann. Rev. Ecol. Syst. 28 (1997) 243–268.
[54] D.P. Faith, Conservation evaluation and phylogenetic diversity, Biol. Conserv. 61 (1992) 1–10.
[55] C.R. Rao, Diversity and dissimilarity coefficients: a unified approach, Theor. Popul. Biol. 21 (1982) 24–43.
[56] C. Ricotta, G.C. Avena, An information-theoretical measure of taxonomic diversity, Acta Biotheor. 51 (2003) 35–41.
[57] C. Ricotta, L. Szeidl, Towards a unifying approach to diversity measures: bridging the gap between the Shannon entropy and Rao's quadratic index, Theor. Popul. Biol. 70 (2006) 237–243.
[58] B. Allen, M. Kon, Y. Bar-Yam, A new phylogenetic diversity measure generalizing the Shannon index and its application to phyllostomid bats, Am. Nat. 174 (2009) 236–243.

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