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Article *in* Journal of Complementary Medicine Research · October 2022

DOI: 10.5455/jcmr.2022.13.04.25

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JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH
Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 13, No. 4, 2022 (pp. 131-149)
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Antioxidants From Sri Lankan Flora: Chemical Diversity and Assessment of Antioxidant Potential

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ABSTRACT

Aim: Medicinal flora is rich with bioactive compounds that exhibit promising antioxidant activities thereby protecting against free radical pathologies leading to health-promoting effects. The use of potent antioxidants is considered a substantial therapeutic approach for the prevention of many of oxidative stress-related diseases. The present review includes details of the reported antioxidant activities of medicinal plant extracts used in Sri Lankan traditional medicine for the treatment of diabetes mellitus, cancer, and kidney disease in the last ten years.

Method: Online databases, Pub Med, Google Scholar, and Science Direct were used for the literature search within the last ten years. The keywords, 'antioxidant activity, 'Sri Lankan flora', '*in vitro* assays', '*in vivo* studies', 'cell-based studies', 'plant extracts', 'fractions', 'isolated compounds', 'diabetes mellitus', 'cancers' and 'kidney diseases' were used in collecting information for the present review.

Results: Of 125 articles, 25 met the inclusion criteria. Among them, 61 medicinal plants were reported in chemical *in vitro* studies, 31 plants were in cell-based *in vitro* studies and five medicinal plants were *in vivo* studies. The results of the present systematic review revealed that most of the reports focused on chemical based *in vitro* studies to determine antioxidant activity, particularly the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay.

Conclusion: Available chemical and cell-based studies suggest that Sri Lankan flora exerts potent antioxidant activities that could contribute as promising sources of antioxidant supplements in therapeutic applications.

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How to cite this article: De Silva WND, Kalansuriya P, Attanayake AP, Arawwawala LDAM. Antioxidants From Sri Lankan Flora: Chemical Diversity and Assessment of Antioxidant Potential. Journal of Complementary Medicine Research, Vol. 13, No. 4, 2022 (pp. 131-149).

INTRODUCTION

Antioxidants can be defined as substances that can inhibit or delay unwanted reactions of oxidation through one or numerous mechanisms (Ahmad, Ijaz, Shabbiri, Ahmed, & Rehman, 2017; Apak, 2019; Nimse & Pal, 2015; Wanigasekera, Joganathan, Pethiyagoda, Yatiwella, & Attanayake, 2019). Depending on the activity of antioxidants, they can be classified as enzymatic or non-enzymatic. Antioxidants act against reactive oxygen species (ROS) and reactive nitrogen species (RNS), thus converting hazardous products to water as the final product (Ahmad, Jaleel, Salem, Nabi, & Sharma, 2010; Aziz, Diab, & Mohammed, 2019; Bunaciu, Aboul-Enein, & Fleschin, 2012; Carocho & Ferreira, 2013). Furthermore, antioxidants inhibit the formation of free radicals via interfering chain reactions (Nimse & Pal, 2015). Endogenous antioxidants such as superoxide dismutase (SOD; EC 1.15. 1.1), catalase (CAT; EC1.11.1.6), glutathione peroxidase (GPx; EC 1.11. 1.9), and exogenous antioxidants such as vitamins, polyphenols, etc. are responsible for conserving or maintaining damages caused by RNS and ROS while maintaining homeostasis. For example, lipid peroxidation can be prevented during vitamin E regeneration by ascorbic acid and glutathione (GSH) (Bouayed & Bohn, 2010). Vitamins, carotenoids, and GSH are classified as small molecule antioxidants that neutralize ROS through a radical scavenging process. SOD, CAT, and albumin as high molecular weight antioxidants can prevent the attack of proteins by neutralizing ROS (Nimse & Pal, 2015). Moreover, antioxidants are classified depending on the occurrence, mode of action, solubility, and location of action as shown in Fig. 1 (Aziz et al., 2019; Carocho & Ferreira, 2013; Nimse & Pal, 2015).

The action of specific defense mechanisms to prevent or inhibit factors that induce oxidative stress is indispensable. Free radicles upon contact with cells, the extracellular matrix, and tissues trigger a series of reactions that activate defense the mechanisms of the body. Numerous mechanisms are involved to remove harmful free radicals and their derivatives from the body. Antioxidants prevent the contact of free radicals and their derivatives with biological substances e.g.; lipid, protein, DNA, and ribonucleic acid (RNA) in the body (Lü, Lin, Yao, & Chen, 2010; Mirończuk-Chodakowska,

KEYWORDS:
Antioxidant,
Cell culture,
In vitro,
Sri Lankan flora.

ARTICLE HISTORY:
Received : Jul 10, 2022
Accepted : Aug 20, 2022
Published: Sep 25, 2022

DOI:
10.5455/jcmr.2022.13.04.25

Witkowska, & Zujko, 2018). Repairing against damaged biomolecules and cells by altering radical oxidation reactions is another defense mechanism against ROS and other free radicals. This mechanism uses enzymes to repair damaged proteins, DNA, oxidized peroxides, and lipids (Sindhi et al., 2013). The tendency to inactivate products produced by free radicals and their derivatives is important in interrupting cell damage. In fact, antioxidant defense mechanisms can be divided into four categories based on the line of defense as first, second, third, and fourth (Aziz et al., 2019; Mirończuk-Chodakowska et al., 2018; Sindhi et al., 2013). Antioxidants related to the first line of defense can prevent or suppress radical species as preventive mechanisms (Sindhi et al., 2013). The antioxidants which can scavenge active radicals for the inhibition and breakage of chain propagation are included under the second line defense mechanism. With the donation of electrons, free radicals reduce their reactivity and become less damaging or neutral (Paramasivam, 2020). Antioxidants in the third-line defense category are involved in repairing damaged biomolecules. They are named *de novo* enzymes (George & Abrahamse, 2020). Activation of free radicals and signals is quenched with the fourth line of antioxidants (Ighodaro & Akinloye, 2018). Antioxidants are involved in most applications because of these defense mechanisms and their efficient activity on free radicals. Antioxidants play an extensive role in food industries, cosmetic industries, and medicinal applications. Among these applications, antioxidants play a vital role in medicinal applications due to their ability to provide protection against free radicals. Antioxidants are important to prevent diseases such as diabetes mellitus, cancer, cardiovascular diseases, aging, neurodegenerative diseases, kidney diseases, etc, (E Obrenovich et al., 2011; Rajendran et al., 2014). When treating diabetes, antioxidants such as N-acetylcysteine, vitamin C, and α-lipoic acid have been reported to play an important role (Bajaj & Khan, 2012). The main reasons for cardiovascular diseases are oxidation of low-density lipoprotein (LDL), oxidative stress which causes vascular inflammation, cardiac hypertrophy, and oxidative stress triggered tissue damage. Antioxidants such as ascorbic acid (vitamin C), α-tocopherol (vitamin E), ubiquinone, and ß-carotene function in the body to reduce LDL oxidation, prevent platelet accumulation, reduce atheromatous lesions, etc. (Sen & Chakraborty, 2011). The main reasons for the occurrence of cancers in the body are oxidative damage to DNA, abnormalities of gene mutations on chromosomes, and activation of the oncogene due to oxidative stress. Antioxidants such as ß-carotene, carotenoids, terpenes, vitamin C, and vitamin E play a major role in the prevention of cancers by inhibiting the damage of DNA, quenching reactions caused to oxidative damage and their adverse effects (Neha, Haider, Pathak, & Yar, 2019; Pizzino et al., 2017; Saeidnia & Abdollahi, 2013). Antioxidants such as polyphenols, carotenoids, vitamin C, and vitamin E have been reported to ameliorate oxidative changes associated with kidney disease. They prevent damage to kidney tissue and produce pro-inflammatory cytokines to protect the kidney for its proper functions in the body (Pizzino et al., 2017). DNA oxidation, mitochondrial dysfunction, and neuronal cell death (due to the formation of toxic products with oxidative stress) lead to the development of neurodegenerative diseases (Liu et al., 2018; Mut-Salud et al., 2016). Furthermore, enzymes (SOD, CAT), ascorbic acid, tocopherols, polyphenols, carotenoids, and coenzyme Q10 could protect against fungus infections and ultraviolet irradiation to

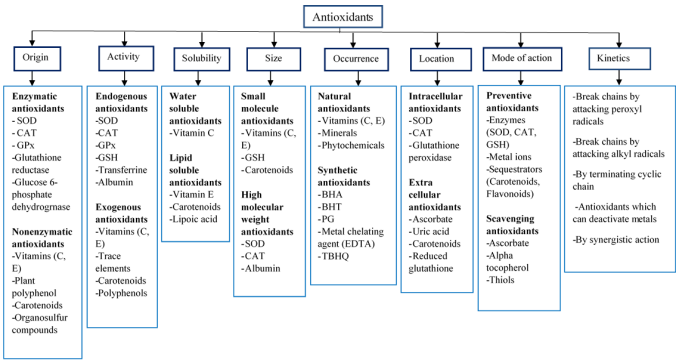

Fig. 1: Classification of antioxidants

overcome macromolecule damage via oxidative stress. It leads to the prevention of aging (Liguori et al., 2018; Liu et al., 2018). Some epidemiological studies suggest that the consumption of plant derived antioxidants have the ability to prevent or reduce the occurrence of these chronic diseases (Hano & Tungmunnithum, 2020; Pandey & Rizvi, 2009). Herbs are used as prominent sources of natural antioxidants due to their wide range of biological effects. Many researchers have investigated phytochemicals in flora including phenolic compounds, flavonoids, sesquiterpenes, coumarins, and other subsidizing compounds as antioxidant agents which can oppose oxidative stress-related diseases for the past few decades (Augustyniak et al., 2010; Justino et al., 2018; Wu et al., 2011; Xu et al., 2017). Investigations were performed using the whole plant or a part of the plant such as leaves, bark, flowers, seeds, fruits, bulbs, roots etc. (Embuscado, 2015; Jayarathna et al., 2016; Navodani, Jayasekara, Soysa, Gooneratne, & Ranathunge, 2019; Padumadasa, Dharmadana, Abeysekera, & Thammitiyagodage, 2016).

Sri Lanka is a hotspot of biodiversity and native Sri Lankan flora consists of about 7,500 plant species and among them, 830 (25%) species are endemic to Sri Lanka (Jayarathna et al., 2016). Owing to high biodiversity, Sri Lanka is blessed with rich medicinal flora where many of the medicinal plants have been enacted for the treatment of oxidative-related diseases as diabetes mellitus, chronic kidney disease, cancer, etc. in traditional medicine. Numerous investigations have been performed on health promoting properties of Sri Lankan flora for the management of diabetes mellitus, cancers, skin diseases and kidney diseases, etc. (Ediriweera & Ratnasooriya, 2009; Kuruppu, Paranagama, & De Silva, 2019; Kuruppu, Paranagama, & Goonasekara, 2019; Napagoda, Malkanthi, Abayawardana, Qader, & Jayasinghe, 2016; Ranasinghe et al., 2013; Samarakoon, Uluwaduge, & Siriwardhene, 2020; Sathasivampillai, Rajamanoharan, Munday, & Heinrich, 2017). For example, antioxidant activity in *Adenanthera pavonina* L., *Thespesia populnea* L., and *Vateria copallifera* (Retz.) Alston, *Schumacheria castaneifolia* Vahl. and *Anthracophyllum lateritium* Berk. were evaluated by many investigators (Fernando, Wijesundera, Soysa, De Silva, & Nanayakkara, 2015; Lindamulage & Soysa, 2016; Samaradivakara et al., 2018; Samarakoon et al., 2017). Based on their investigations, it has been suggested that the mentioned Sri Lankan medicinal plants could be used for the treatment of cancers due to their antioxidant potential mainly due to the presence of polyphenolic compounds and flavonoids. Moreover, antidiabetic activity was assessed in medicinal plants such as *Vateria copallifera*

(Retz.) Alston, *Tinospora cordifolia* (Willd.), *Costus speciosus* (Koen ex.Retz.) (Perera et al., 2018; Samaradivakara et al., 2018; Samarakoon, Lakmal, Kim, & Jeon, 2014). However, screening of antioxidant potential of medicinal plant extracts has become a foremost interest in ethnopharmacological research, particularly for the plants that have been used for the treatment of diabetes mellitus, cancer, and kidney disease in Sri Lankan traditional medicine.

Several articles have discussed about the biodiversity and their importance of Sri Lankan herbs with therapeutic effects and bioactive compounds isolated from Sri Lankan flora (Gunawardana & Jayasuriya, 2019; Jayasinghe et al., 2017; Jesuthasan & Uluwaduge, 2017; Siriwardhana, Wijesundara & Karunaratne, 2015). Although several articles were published on Sri Lankan flora, antioxidant activity, chemical and cellular studies targeting oxidative stress-related diseases, i.e. cancer, kidney disease, and diabetes mellitus, these have not been reviewed in detail to date. Herein, we attempt to discuss the reported antioxidant activity of natural products such as crude extracts, fractions, and isolated compounds that have been used in related to the Sri Lankan traditional medicine applications of diabetes mellitus, chronic kidney disease, and cancer using *in vitro* and *in vivo* models of testing.

METHODOLOGY

The literature review was conducted on general thematic headings via the Ovid interface, PubMed, Google Scholar, and Science Direct. The articles were selected based on keywords and methodological filters under search strategy. The search keywords were as follows. 'Antioxidant activity', 'Sri Lankan flora', '*in vitro* assays', '*in vivo* studies', 'plant extracts', 'fractions', 'isolated compounds', 'diabetes mellitus', 'cancers' and 'kidney diseases'. As methodological filters, *in vivo*, *in vitro*, chemical, and cell-based assays on antioxidant activity of the flora were selected. The selection of articles was limited to the past ten year period (2011 to 2021). The present review describes the studies conducted on the investigation of antioxidant activities of extracts, fractions, and compounds derived from Sri Lankan medicinal plants using *in vitro*, cell-based, and *in vivo* studies. By the first selection based on the inclusion criteria given, a total of 6280 articles were selected. Out of them, 1803 were excluded for being duplicates. After applying the inclusion criteria, there were 125 articles remaining. A total of 25 articles were included for this systematic review (Fig. 2). The reported antioxidant activities of natural products were classified into ways of evaluating such as *in vitro*, *in vivo*, and cell-based studies.

RESULTS

In vitro chemical-based assays

The antioxidant activities of plant extracts, fractio ns, and compounds were tested in many *in vitro* assays (Kasote, Katyare, Hegde, & Bae, 2015; Oroian & Escriche, 2015). Although numerous methods have been established to determine the antioxidant activity, their response to test samples could vary due to various thermodynamic and kinetic activities (Apak, 2019). Among the developed antioxidant assays, 1,1- diphenyl-2-picrylhydrazyl (DPHH) free radical scavenging, ferric reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC), and 2,2'-azinobis-(3-ethyl-benzothiazoline-6- sulphonic acid (ABTS) assays were widely used to determine the antioxidant potentials of crude extracts, fractions, and compounds derived from Sri Lankan medicinal plants (Amarasiri, Attanayake, Arawwawala, Jayatilaka, & Mudduwa, 2020; Attanayake & Jayatilaka, 2016; Jayathilake, Rizliya, & Liyanage, 2016; Samarakoon et al., 2014). All selected articles reported DPPH assay for the determination of *in vitro* antioxidant activity of most natural products. Percentages of other assays (ABTS, ORAC, FRAP, NO, and FIC) are reported as follows (Figure 3). Details on the antioxidant activity of 61 Sri Lankan plants are listed in Tables 1 and 2.

In addition to the medicinal plants listed in Table 1 and 2, Weerasingha and Deraniyagala (2016) reported nine endemic Sri Lankan plants with potent antioxidant activities. Methanol extracts of *Garcinia zeylanica* Roxb. (leaves, bark, and stem), *Plectranthus zeylanicus Benth.* (leaves, stem, bark, shoots, and roots), *Argyreia populifolia* Choisy. (leaves, stem, bark, shoots, and roots), *Dipterocarpus zeylanicus* Thw. (heartwood), *Garcinia quaestia* L. (leaves, bark, stem), *Vernonia zeylanica* L. (Less) (leaves, stem, bark), *Horsfieldia iryaghedhi* (Gaertn.) Warb. (bark), *Dialium ovoideum* Thw. (leaves, bark), *Canarium zeylanicum* (Retz.) Blume (bark) were screened using DPPH and FRAP assays (Weerasinghe & Deraniyagala, 2016). Quercetin (1) and catechin (2) were isolated from the chloroform extract of *Mangifera zeylanica* Hook. bark using a silica gel column (Fig. 4). The inhibitory activities of quercetin (1) and catechin (2) in the DPPH assay were obtained as IC_{50} values of 33.1± 0.59 µM and 34.0± 0.63 µM respectively

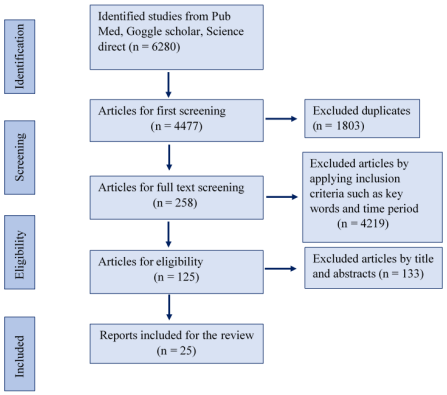

Fig. 2: Flow diagram: identification, screening and selection of articles

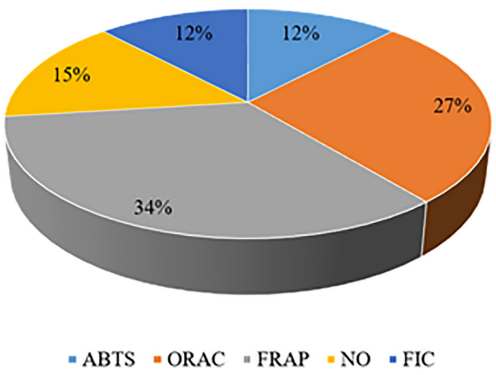

Fig. 3: Graphical representation for reported assays in selected articles

Table 1: List of medicinal plants used in Sri Lankan traditional medicine for the treatment of cancers, diabetes mellitus and kidney diseases with reported antioxidant potentials screened using DPPH *in vitro* assay

Plant name/family	*Part of the plant*	*Extract/fraction*	*IC_{50} values of DPPH assay*	*Reference*
Medicinal plants used for the management of cancers				
Annona muricata L. (Annonaceae)	leaf	aqueous	411.14 ± 120.90 µg/mL	(Navodani et al, 2019)
	root	aqueous	1006.69 ± 49.13 µg/mL	
	leaf	aqueous	200.51 ± 45.72 µg/mL	
Bhesa ceylanica Thw. (Celastraceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	> 1000 µg/mL	
		MeOH	146.20 ± 0.4 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	375.00 ± 0.1 µg/mL	
		MeOH	1.04 ± 0.01 µg/mL	
Calophyllum calaba L. (Calophyllaceae)	leaf	hexane	353.10 ± 0.2 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	279.90 ± 0.4 µg/mL	
		EtOAc	12.99 ± 0.3 µg/mL	
		MeOH	10.95 ± 0.1 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	383.20 ± 0.1 µg/mL	
		EtOAc	237.70 ± 0.1 µg/mL	
		MeOH	90.25 ± 0.2 µg/mL	
Calophyllum moonii Wight. (Guttiferae)	leaf	hexane	1.66 ± 0.02 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	64.69 ± 0.2 µg/mL	
		MeOH	18.27 ± 0.3 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	144.80 ± 0.3 µg/mL	
		EtOAc	74.87 ± 0.4 µg/mL	
		MeOH	6.99 ± 0.2 µg/mL	
Calophyllum tomentosum Wight. (Calophyllaceae)	leaf	hexane	309.20 ± 0.3 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	287.80 ± 0.1 µg/mL	
		EtOAc	4.03 ± 0.1 µg/mL	
		MeOH	1.53 ± 0.01 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		MeOH	10.55 ± 0.1 µg/mL	
		hexane	1.75 ± 0.04 µg/mL	
Campnosperma zeylanica Thw. (Anacardiaceae)	leaf	hexane	224.80 ± 0.3 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	256.70 ± 0.4 µg/mL	
		EtOAc	16.89 ± 0.1 µg/mL	
		MeOH	10.64 ± 0.3 µg/mL	
	bark	hexane	290.80 ± 0.3 µg/mL	
		$CHCl_3$	291.00 ± 0.2 µg/mL	
		EtOAc	21.45 ± 0.1 µg/mL	
		MeOH	17.85 ± 0.2 µg/mL	

Plant name/family	*Part of the plant*	*Extract/fraction*	*IC_{50} values of DPPH assay*	*Reference*
		Medicinal plants used for the management of cancers		
Chaetocarpus coriaceus Rich. (Euphorbiaceae)	leaf	hexane	238.10 ± 0.2 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	844.00 ± 0.4 µg/mL	
		MeOH	12.88 ± 0.3 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	378.70 ± 0.3 µg/mL	
		EtOAc	27.70 ± 0.2 µg/mL	
		MeOH	18.97 ± 0.3 µg/mL	
Cleistocalyx nervosum Var. (Myrtaceae)	leaf	hexane	302.10 ± 0.2 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	354.85 ± 0.1 µg/mL	
		EtOAc	458.90 ± 0.3 µg/mL	
		MeOH	399.20 ± 0.2 µg/mL	
	bark	hexane	315.80 ± 0.3 µg/mL	
		$CHCl_3$	348.90 ± 0.2 µg/mL	
		EtOAc	436.01 ± 0.4 µg/mL	
		MeOH	389.50 ± 0.4 µg/mL	
Cocos nucifera L. Var. (aurantiaca)	whole plant	EtOAc soluble proanthocyanidins	11.02 ± 0.60 µg/mL	(Padumadasa et al., 2016)
Coleus amboinicus Lour. (Lamiaceae)	leaf	aqueous	57.10 ± 0.98 µg/mL	(Navodani et al., 2019)
Connarus championii Thw, (Connaraceae)	leaf	hexane	242 .60 ± 0.3 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	349.90 ± 0.4 µg/mL	
		EtOAc	8.67 ± 0.2 µg/mL	
		MeOH	5.68 ± 0.2 µg/mL	
	bark	hexane	474.10 ± 0.2 µg/mL	
		$CHCl_3$	715.00 ± 0.3 µg/mL	
		EtOAc	217.00 ± 0.3 µg/mL	
		MeOH	1.69 ± 0.02 µg/mL	
Doona macrophylla Thw. (Dipterocarpaceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	94.65 ± 0.2 µg/mL	
		MeOH	16.24 ± 0.3 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	36.78 ± 0.2 µg/mL	
		MeOH	1.12 ± 0.03 µg/mL	
Flueggea leucopyrus Willd. (Phylanthreceae)	leaf	MeOH	402.58 ± 3.97 µg/mL	(Bulugahapitiya & Munasinghe, 2020)
Gardenia crameri Tirveng. (Rubiaceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	219.80 ± 0.3 µg/mL	
		MeOH	> 1000 µg/mL	
	bark	hexane	854.10 ± 0.2 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	> 1000 µg/mL	
		MeOH	16.21 ± 0.4 µg/mL	

Plant name/family	*Part of the plant*	*Extract/fraction*	*IC_{50} values of DPPH assay*	*Reference*
Medicinal plants used for the management of cancers				
Actinodaphne stenophylla Thw. (Lauraceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	961.80 ± 0.2 µg/mL	
		EtOAc	47.13 ± 0.4 µg/mL	
		MeOH	2 7.17 ± 0.2 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	> 1000 µg/mL	
		MeOH	> 1000 µg/mL	
Lijndenia capitellata (Arn.) K. Bremer (Melastomaceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	12.18 ± 0.2 µg/mL	
		MeOH	10.55 ± 0.3 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	180.40 ± 0.4 µg/mL	
		MeOH	11.42 ± 0.2 µg/mL	
Malvaviscus penduliflorus Var. (Malvaceae)	flower	aqueous	644.78 ± 37.74 µg/mL	(Navodani et al., 2019)
	leaf	aqueous	35.41 ± 4.20 µg/mL	
Mangifera zeylanica Hook.f. (Anacardiaceae)	bark	quercetin	33.1 ± 0.59 µM	(Ediriweera et al., 2016)
	bark	catechin	34.0 ± 0.63 µM	
Memecylon rostratum Thw. (Melastomataceae)	leaf	hexane	100.20 ± 0.3 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	565.30 ± 0.1 µg/mL	
		EtOAc	6.07 ± 0.2 µg/mL	
		MeOH	4.19 ± 0.3 µg/mL	
	bark	hexane	74.57 ± 0.2 µg/mL	
		$CHCl_3$	218.80 ± 0.4 µg/mL	
		EtOAc	1.2 ± 0.02 µg/mL	
		MeOH	8.93 ± 0.1 µg/mL	
Munronia pinnata (Wall.) Theob (Meliaceae)	leaf	aqueous	1229.13 ± 79.14 µg/mL	(Navodani et al., 2019)
	flower	aqueous	100.42 ± 20.52 µg/mL	
Nepenthes distillatorya L. (Nepenthaceae)	leaf	hexane	1 17.80 ± 0.4 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	3.56 ± 0.3 µg/mL	
		EtOAc	64.47 ± 0.4 µg/mL	
		MeOH	1.08 ± 0.01 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	66.10 ± 0.2 µg/mL	
		MeOH	1.7 ± 0.01 µg/mL	
Ochna jabotapita L. (Ochnaceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	149.50 ± 0.2 µg/mL	
		MeOH	2.66 ± 0.04 µg/mL	

Plant name/family	*Part of the plant*	*Extract/fraction*	*IC_{50} values of DPPH assay*	*Reference*
Medicinal plants used for the management of cancers				
	bark	hexane	645.10± 0.2 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	> 1000 µg/mL	
		MeOH	31.26± 0.3 µg/mL	
Rauvolfia serpentia Benth. (Apocynaceae)	whole plant	aqueous	845.15 ± 40.21 µg/mL	(Navodani et al., 2019)
	leaf	aqueous	188.22 ± 24.30 µg/mL	
Schumacheria castaneifolia L. (Dilleniaceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	> 1000 µg/mL	
		MeOH	87.35± 0.3 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	525.30 ± 0.3 µg/mL	
		MeOH	1 1.60 ± 0.2 µg/mL	
Semecarpus subpeltata Thw. (Anacardiaceae)	leaf	hexane	146.70± 0.2 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	267.50± 0.3 µg/mL	
		MeOH	35.67± 0.2 µg/mL	
	bark	hexane	>1000 µg/mL	
		$CHCl_3$	>1000 µg/mL	
		EtOAc	175.30± 0.1 µg/mL	
		MeOH	151.30± 0.2 µg/mL	
Vateria copallifera (Retz.) Alston (Dipterovarpaceae)	bark	hexane	10.90%	(Samaradivakara et al., 2018)
		EtOAc	173.8 ± 4.0 µg/mL	
		EtOH	114.8 ± 1.7 µg/mL	
		vateriferol	Not detected	
Vateria copallifera (Retz.) Alston (Dipterocarpaceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	96.64± 0.2 µg/mL	
		MeOH	98.76± 0.1 µg/mL	
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	110.60± 0.3 µg/mL	
		MeOH	86.74± 0.1 µg/mL	
Vernonia cinerea L. (Asteraceae)	whole plant	aqueous	120.32 ± 4.25 µg/mL	(Navodani et al., 2019)
	aerial parts	aqueous	391.64 ± 27.05 µg/mL	
Wendlandia bicuspidate L. (Rubiaceae)	leaf	hexane	> 1000 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	> 1000 µg/mL	
		MeOH	19.15± 0.1 µg/mL	
Wrightia zeylanica (L.) R. Br. (Apocynaceae)	leaf	hexane	626.20± 0.3 µg/mL	(Jayarathna et al., 2016)
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	974.90± 0.4 µg/mL	
		MeOH	584.00± 0.2 µg/mL	

Plant name/family	*Part of the plant*	*Extract/fraction*	*IC_{50} values of DPPH assay*	*Reference*
Medicinal plants used for the management of cancers				
	bark	hexane	> 1000 µg/mL	
		$CHCl_3$	> 1000 µg/mL	
		EtOAc	> 1000 µg/mL	
		MeOH	553.50 ± 0.2 µg/mL	
Medicinal plants used for the management of diabetes mellitus				
Aerva lanata (L.) Juss. (Amaranthaceae)	roots	aqueous	211.94 ± 16.73 µg/mL	(Attanayake & Jayatilaka, 2016)
Azadirachta indica A.Juss. (Meliaceae)	leaf	aqueous	133.76 ± 1.58 µg/mL	(Attanayake & Jayatilaka, 2016)
Benincasa hispida (Thunb.) Cogn. (Cucurbitaceae)	fruit	aqueous	157.80 ± 1.58 µg/mL	
Coccinia grandis L. voigt (Cucurbitaceae)	leaf	MeOH	262.48 ± 3.02 µg/mL	(Galketiya et al., 2017)
Costus speciosus Koen. (Costaceae)	leaf	MeOH	0.320 ± 0.01 mg/mL	(Samarakoon et al., 2014)
		n-hexane	0.607 ± 0.02 mg/mL	
		$CHCl_3$	0.639 ± 0.05 mg/mL	(Galketiya et al., 2017)
		EtOAc	0.403 ± 0.02 mg/mL	
		aqueous	0.110 ± 0.01 mg/mL	
		MeOH	4.63 ± 0.13 µg/mL	
Coscinium fenestratum (Goetgh.) Colebr. (Menispermaceae)	wood	aqueous	121.30 ± 1.45 µg/mL	(Attanayake & Jayatilaka, 2016)
Cynometra cauliflora L. (Fabaceae)	leaf	EtOH	12.46 ± 0.22 µg/mL	(Perera, Samarasekera, Handunnetti, & Weerasena, 2016)
Dregea volubilis (L.f.) Benth. ex Hook.f. (Asclepidaceae)	whole plant	aqueous	139.06 ± 2.00 µg/mL	(Attanayake & Jayatilaka, 2016)
Gmelina arborea Linn. (Verbenaceae)	bark	aqueous	36.89 ± 1.23 µg/mL	(Attanayake, Jayatilaka, Pathirana, & Mudduwa, 2015a)
Gracilaria edulis (Gmel.) Silva. (Gracilariaceae)	whole plant	MeOH	3.19 ± 0.02 mg/mL	(Gunathilaka et al., 2019)
		hexane fraction	6.22 ± 0.01 mg/mL	
		$CHCl_3$	3.29 ± 0.02 mg/mL	
		EtOAc	3.17 ± 0.04 mg/mL	
		aqueous fraction	3.91 ± 0.03 mg/mL	
Ipomoea aquatic Forssk. (Convolvulaceae)	leaf, stems	MeOH	22.20 ± 0.45 µg/mL	(Galketiya et al., 2017)
Kokoona zeylanica Thw. (Celastraceae)	bark	aqueous	101.27 ± 2.19 µg/mL	(Attanayake & Jayatilaka, 2016)
Languas galanga (Linn.) Stuntz (Zingiberaceae)	root	aqueous	77.39 ± 2.50 µg/mL	(Attanayake, Jayatilaka, Pathirana, & Mudduwa, 2015b)
Mommordica charantia Linn (Cucurbitaceae)	fruit	aqueous	67.25 ± 2.12 µg/mL	(Attanayake et al., 2015b)
Murraya koenigii L. (Rutaceae)	leaf	EtOH	18.95 ± 0.46 µg/mL	(Perera et al., 2016)
Nigella sativa L. (Ranunculaceae)	seeds	aqueous	158.28 ± 2.00 µg/mL	(Attanayake et al., 2018)
Nyctanthus arbo-tristis Linn (Oleacea)	flowers	aqueous	55.23 ± 1.23 µg/mL	(Attanayake et al., 2015b)

Plant name/family	*Part of the plant*	*Extract/fraction*	*IC_{50} values of DPPH assay*	*Reference*
		Medicinal plants used for the management of diabetes		
Olax zeylanica L. (Olacaceae)	leaf	MeOH	30.88 ± 0.62 µg/mL	(Attanayake & Jayatilaka, 2016)
	aerial part	aqueous	53.35± 1.15 µg/mL	(Attanayake & Jayatilaka, 2016)
Psidium guajava L. (Myrtaceae)	leaf	EtOH	16.58 ± 0.38 µg/mL	(Perera et al., 2016)
Scoparia dulcis L. (Scrophulariaceae)	leaf, stem	MeOH	109.06 ± 0.21 µg/mL	(Galketiya et al., 2017)
Sida alnifolia Linn. (Malvaceae)	Leaf	aqueous	63.14± 0.98 µg/mL	(Attanayake et al., 2018)
Spondias dulcis L. (Anacardiaceae)	leaf	EtOH	26.67 ± 2.11 µg/mL	(Perera et al., 2018)
Spondias pinnata Kurz. (Anacardiaceae)	bark	aqueous	42.06± 0.19 µg/mL	(Attanayake et al., 2015b)
	bark	aqueous	59.23± 1.02 µg/mL	(Attanayake et al., 2015b)
Syzygium caryophyllatum (Linn.) Als. (Myrtaceae)	leaf	pulverized material	500.20 ± 44.33 µg/mL	
		EtOAc	91.20 ± 4.28 µg/mL	
	fruits	aqueous	251.05 ± 17.52 µg/mL	(Wathsara et al., 2020)
		pulverized material	873.72 ± 12.52 µg/mL	
		hexane	100.97 ± 8.19 µg/mL	
		EtOAc	135.53 ± 9.83 µg/mL	
		aqueous	946.42 ± 65.04 µg/mL	
Syzygium cumini (L.) Skeels (Myrtaceae)	bark	aqueous	19.48± 1.01 µg/mL	(Attanayake et al., 2018)
Tinospora cordifolia (Willd.) (Menispermaceae)	bark	MeOH	389.20 ± 0.75µg/mL	(Perera et al., 2018)
Trichosanthes cucumerina L. (Cucurbitaceae)	aerial	aqueous	39.2± 0.2 µg/mL	(Arawwawala et al., 2011)
		EtOH	15.7± 0.6 µg/mL	
		Medicinal plants used for the management of kidney diseases		
Abelmoschus moschatus Medik. (Malvaceae)	leaf	aqueous	15.99 ± 0.64 (mg trolox/g of extract)	(Amarasiri et al., 2020)
Asparagus falcatus L. (Asparagaceae)	leaf	aqueous	27.92 ± 0.41(mg trolox/g of extract)	
Barleria prionitis Linn. (Acanthaceae)	whole plant	aqueous	148.83 ± 2.11(mg trolox/g of extract)	

IC_{50}, concentration of compound where percent inhibition is equal to 50; DPPH assay, 1,1-diphenyl-2-picrylhydrazyl) free radical scavenging assay; $CHCl_3$, chloroform; EtOAc, ethyl acetate; MeOH, methanol; EtOH, ethanol

Table 2: List of medicinal plants used Sri Lankan traditional medicine for the treatment of cancers, diabetes mellitus and kidney diseases with reported antioxidant potentials screened using ABTS, ORAC, FRAP, NO and FIC *in vitro* assays

			IC_{50} values					
Plant name/family	*Part of the plant*	*Extract/fraction*	*ABTS*	*ORAC*	*FRAP*	*NO*	*FIC*	*Reference*
			Medicinal plants used for the management of cancers					
Annona muricata L. (Annonaceae)	leaf	aqueous	-	-	70.97 ± 1.02 µg/mL	-	-	(Navodani et al., 2019)
Coleus amboinicus Lour. (Lamiaceae)	leaf	aqueous	-	-	49.82 ± 3.07 µg/mL	-	-	(Navodani et al., 2019)
Flueggea leucopyrus Willd. (Phylanthreceae)	leaf	MeOH	-	148.65 ± 11.91 µg/mL	-	-	-	(Bulugahapitiya & Munasinghe, 2020)

Plant name/family	Part of the plant	Extract/ fraction	IC_{50} values					Reference
			ABTS	ORAC	FRAP	NO	FIC	
Malvaviscus penduliflorus Var. (Malvaceae)	flower	aqueous	-	-	99.08 ± 12.52 µg/mL	-	-	(Navodani et al., 2019)
Munronia pinnata (Wall.) Theob (Meliaceae)	leaf	aqueous	-	-	182.69 ± 19.52 µg/mL	-	-	(Navodani et al., 2019)
Rauvolfia serpentia Benth. (Apocynaceae)	whole plant	aqueous	-	-	175.82 ± 28.70 µg/mL	-	-	(Navodani et al., 2019)
Vateria copallifera (Retz.) Alston (Dipterovarpaceae)	bark	hexane	-	Not detected at 3 µg/mL	-	-	-	(Samaradivakara et al., 2018)
		EtOAc	-	2966.9 ± 0.2 µg/mL	-	-	-	
		EtOH	-	4700.8 ± 0.2 µg/mL	-	-	-	
		vateriferol	-	2079.0 ± 0.2 mg TE/g of extract	-	-	-	
Vernonia cinerea L. (Asteraceae)	whole plant	aqueous	-	-	317.35 ± 23.55 µg/mL	-	-	(Navodani et al., 2019)
	aerial parts	aqueous	-	-	427.23 ± 31.63 µg/mL	-	-	
Medicinal plants used for the management of diabetes mellitus								
Aerva lanata (L.) Juss. (Amaranthaceae)	roots	aqueous	-	-	2.12 ± 0.07 µM	346.87 ± 3.02 µg/mL	-	(Attanayake & Jayatilaka, 2016)
Azadirachta indica A.Juss. (Meliaceae)	leaf	aqueous	-	-	4.82 ± 0.23 µM	250.52 ± 2.34 µg/mL	-	(Attanayake & Jayatilaka, 2016)
Benincasa hispida (Thunb.) Cogn. (Cucurbitaceae)	fruit	aqueous	-	-	2.23 ± 0.08 µM	475.26 ± 3.56 µg/mL	-	(Attanayake & Jayatilaka, 2016)
Coccinia grandis L. voigt (Cucurbitaceae)	leaf	MeOH	-	-	5.93 ± 0.34 µM	168.30 ± 1.03 µg/mL	-	(Galketiya et al., 2017)
Coscinium fenestratum (Goetgh.) Colebr. (Menispermaceae)	wood	aqueous	-	-	2.74 ± 0.16 µM	481.38 ± 3.30 µg/mL	-	(Attanayake & Jayatilaka, 2016)
Cynometra cauliflor L. (Fabaceae)	leaf	EtOH	-	1317 ± 127 µg/mL	2760 ± 12 µg/mL	-	15.67 ± 0.48 µg/mL	(Perera et al., 2016)
Dregea volubilis (L.f.) Benth. ex Hook.f. (Asclepidaceae)	whole plant	aqueous	-	-	1.63 ± 0.89 µM	460.21 ± 4.05 µg/mL	-	(Attanayake & Jayatilaka, 2016)
Gmelina arborea Linn. (Verbenaceae)	bark	aqueous	-	-	8.98 ± 0.09 µM	139.56 ± 4.20 µg/mL	-	(Attanayake et al., 2015a)
Gracilaria edulis (Gmel.) Silva. (Gracilariaceae)	whole pant	MeOH	0.56 ± 0.01 µg/mL	1.61 ± 0.19 µg/mL	0.26 ± 0.03 µg/mL	-	9.23 ± 0.19 µg/mL	(Gunathilaka et al., 2019)
		hexane fraction	0.54 ± 0.01 µg/mL	0.57 ± 0.07 µg/mL	1.93 ± 0.35 µg/mL	-	2.58 ± 0.03 µg/mL	
		$CHCl_3$	0.44 ± 0.01 µg/mL	0.77 ± 0.05 µg/mL	2.19 ± 0.23 µg/mL	-	2.43 ± 0.01 µg/mL	

Plant name/family	Part of the plant	Extract/ fraction	IC_{50} values					Reference
			ABTS	ORAC	FRAP	NO	FIC	
		EtOAc	0.41 ± 0.02 µg/mL	1.44 ± 0.29 µg/mL	8.51 ± 0.09 µg/mL	-	2.22 ± 0.01 µg/mL	
		aqueous fraction	0.45 ± 0.03 µg/mL	0.44 ± 0.09 µg/mL	1.23 ± 0.21 µg/mL	-	2.71 ± 0.02 µg/mL	
Ipomoea aquatic Forssk. (Convolvulaceae)	leaf, stems	MeOH	-	-	-	-	-	(Galketiya et al., 2017)
Kokoona zeylanica Thw. (Celastraceae)	bark	aqueous	-	-	0.12 ± 0.01 µM	419.93 ± 2.64 µg/mL	-	(Attanayake & Jayatilaka, 2016)
Languas galanga (Linn.) Stuntz (Zingiberaceae)	root	aqueous	-	-	1.24 ± 0.05 µM	327.88 ± 2.98 µg/mL	-	(Attanayake et al., 2015b)
Mommordica charantia Linn (Cucurbitaceae)	fruit	aqueous	-	-	1.25 ± 0.10 µM	236.72 ± 4.52 µg/mL	-	(Attanayake et al., 2015b)
Murraya koenigii L. (Rutaceae)	leaf	EtOH	-	746.0 ± 31.8 µg/mL	370.8 ± 2 µg/mL	-	12.57 ± 0.88 µg/mL	(Perera et al., 2016)
Nigella sativa L. (Ranunculaceae)	seeds	aqueous	-	-	1.25 ± 0.45 µM	381.85 ± 2.45 µg/mL	-	(Attanayake et al., 2018)
Nyctanthus arbo-tristis Linn (Oleacea)	flowers	aqueous	-	-	2.85 ± 0.52 µM	241.23 ± 1.80 µg/mL	-	(Attanayake et al., 2015b)
Psidium guajava L. (Myrtaceae)	leaf	EtOH	-	936.5 ± 63.5 µg/mL	2258 ± 11 µg/mL	-	2684 ± 34 µg/mL	(Perera et al., 2016)
Sida alnifolia Linn. (Malvaceae)	leaf	aqueous	-	-	1.69 ± 0.32 µM	262.18 ± 1.02 µg/mL	-	(Attanayake et al., 2018)
Spondias dulcis L. (Anacardiaceae)	leaf	EtOH	-	507.9 ± 57.8 µg/mL	1418 ± 2 µg/mL	-	2350 ± 89 µg/mL	(Perera et al., 2018)
Spondias pinnata Kurz. (Anacardiaceae)	bark	aqueous	-	-	3.91 ± 0.57 µM	176.00 ± 4.43 µg/mL	-	(Attanayake et al., 2015b)
Syzygium caryophyllatum (Linn.) Als. (Myrtaceae)	bark	aqueous	-	-	4.32 ± 0.38 µM	199.56 ± 1.23 µg/mL	-	(Attanayake et al., 2015b)
	leaf	pulverized material	33.2 ± 1.68 µg/mL	221.00 ± 34.96 mg TE/g	48.27 ± 8.11 mg TE/g	-	-	(Wathsara et al., 2020)
		EtOAc	40.61 ± 2.76 µg/mL	344.31 ± 3.37 mg TE/g	262.26 ± 43.93 mg TE/g	-	-	
		aqueous	27.04 ± 2.06 µg/mL	320.97 ± 20.62 mg TE/g	73.42 ± 12.58 mg TE/g	-	-	
	fruits	pulverized material	13.73 ± 0.69 µg/mL	45.98 ± 2.58 mg TE/g	6.81 ± 1.17 mg TE/g	-	-	
		hexane	15.01 ± 0.65 µg/mL	32.77 ± 1.41 mg TE/g	53.91 ± 12.30 mg TE/g	-	-	
		EtOAc	89.54 ± 3.88 µg/mL	118.65 ± 7.60 mg TE/g	63.07 ± 10.17 mg TE/g	-	-	

Plant name/family	Part of the plant	Extract/ fraction	IC_{50} values					Reference
			ABTS	ORAC	FRAP	NO	FIC	
		aqueous	31.45 ± 1.45 µg/ mL	20.93 ± 4.49 mg TE/g	15.45 ± 0.68 mg TE/g	-	-	
Syzygium cumini (L.) Skeels (Myrtaceae)	bark	aqueous	-	-	26.06± 0.10 µM	103.35± 1.23 µg/mL	-	(Attanayake et al., 2018)
Tinospora cordifolia (Willd.) (Menispermaceae)	bark	MeOH	-	121.29 ± 2.12 mg TE/g	586.66 ± 3.29 mg TE/g	-	100–5000 µg/mL	(Perera et al., 2018)
Medicinal plants used for the management of kidney diseases								
Abelmoschus moschatus Medik. (Malvaceae)	leaf	aqueous	73.02 ± 0.65(mg trolox/g of extract)	94.25 ± 13.03(mg trolox/g of extract)	-	-	-	(Amarasiri et al., 2020)
Asparagus falcatus L. (Asparagaceae)	leaf	aqueous	134.14 ± 2.91(mg trolox/g of extract)	108.46 ± 14.72(mg trolox/g of extract)	-	-	-	
Barleria prionitis Linn. (Acanthaceae)	whole plant	aqueous	182.68 ± 5.37(mg trolox/g of extract)	111.83 ± 7.76(mg trolox/g of extract)	-	-	-	

IC_{50}, concentration of compound where percent inhibition is equal to 50; ABTS, {2,2'– azinobis-(3-ethyl-benzothiazoline-6-sulphonic acid)} assay; FRAP, ferric reducing antioxidant power; NO, nitric oxide; FIC, ferrous ion chelating; CHCl3, chloroform; EtOAc, ethyl acetate; MeOH, methanol; EtOH, ethanol

(Ediriweera et al., 2016). Vateriferol (3) was isolated from the *Vateria copallifera* (Retz.) Alston using a silica gel column (Fig. 4). Vaterferol (3) exhibited an IC_{50} value of 2079.0 ± 0.2 mg trolox/g of extract in ORAC assay (Samaradivakara et al., 2018). Medicinal plant extracts and bioactive compounds that have been used for the management of diabetes mellitus were reviewed by Samarakoon et al. (2018). Active compounds such as costunolide (4) and eremanthin (5) from *Costus specious* (Koen.), thymoquinone (6) from *Nigella sativa* L., quercetin-3-*O*-glucoside (7) and quercetin-3-*O*-(6"-malonyl-glucoside) (8) from *Moringa oleifer* Lam., apigenin-6-C-β-L-fucopyranoside (9) (Fig. 4) and apigenin-6-C-(2"-*O*-α-L-rhamnopyranosyl)-β-L-fucopyranoside (10) from *Averrhoa carambola* L., α-spinasterol (11) and stigmasterol (12) from *Alternanthera sessilis* L. (Fig. 5) and quercetin-3-*O*-glucoside (7) from *Annona squamosal* Linn. were identified as potential candidates for drug leads targeting the treatment of diabetes mellitus due to their antioxidant activities (Samarakoon et al., 2020).

In vitro cell-based assays

The *in vitro* cell-based studies have been performed to elucidate the cellular antioxidative mechanisms. Cell types are compromised with model systems which are related to the pathogenesis of diseases while it could be used to evaluate the antioxidant effects (Niki, 2010). Sri Lankan medicinal plants that have been used for the treatment of cancers and diabetes mellitus with reported antioxidant activity screened using cell culture based assays are mentioned in Table 3.

In vivo studies

Functionality and efficacy of phytochemicals and their bioactivities were investigated by evaluating antioxidant activities using different antioxidants and enzymes i.e., reduced glutathione, SOD, glutathione peroxidase *in vivo*. Furthermore, glutathione-S-transferase (GST), γ-glutamyl transpeptidase activity (GGT) assays, and plasma ferric reducing capacity were used to evaluate antioxidant activities (Alam, Bristi, & Rafiquzzaman, 2013; Sharifi-Rad et al., 2018). Aqueous aerial part extracts of *Trichosanthes cucumerina* L. were administered orally for 14 consecutive days at a therapeutic dose of 750 mg/kg to Wistar rats. Oxidative stress was induced by CCl_4 (1 mL/kg). A reduction in formation of lipid peroxidation products was reported as 30.5% and 33.8% with the treatment of aqueous and EtOH extracts respectively compared to the CCl_4 treated Wistar rats (Arawwawala, Thabrew, & Arambewela, 2011). In addition, *Coccinia grandis* (L) voigt, *Gmelina arborea* Roxb. *Spondias pinnata* (Linn. f.) Kurz were studied for their antioxidant activity in streptozotocin-induced diabetic rats. Studies were performed on the treatment of aqueous bark extracts of *G. arborea* (1.00 g/kg), *S. pinnata* (1.00 g/kg), and *C. grandis* leaves extract (0.75 g/kg) for 30 days. The results revealed that the extracts had potent antioxidant activities *in vivo*. The level of antioxidant enzymes were as follws; 49% in glutathione reductase, 23% in GPx, 68% in glutathione S-transferase and 29% in GSH, 44% reduction in malondialdehyde in *G. arborea* treated diabetic rats (Attanayake, Jayatilaka, Mudduwa, & Pathirana, 2018). Furthermore, Sri Lankan broken orange pekoe fannings (BOPF) grade black tea (*Camellia sinensis* L.) was examined using rat model to determine antioxidant activity in terms of high, mid, and low grown climatic elevations. The black tea infusions were administrated (480 mg/mL) orally for 30 days. Antioxidant activity of *C. sinensis in vivo* was reported as the percentile of DPPH radicals (high grown; 70.55 ± 0.28%, mid grown;

Table 3: List of medicinal plants used Sri Lankan traditional medicine for the treatment of cancers and diabetes mellitus with reported antioxidant potentials screened using cell-based assays

Name of the plant	*Part of the plant*	*Extract*	*Cell line*	*Reference*
		Medicinal plants used for the management of cancers		
Actinodaphne stenophylla Thw. (Lauraceae)	leaf/bark	hexane,$CHCl_3$,EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Adenanthera pavonina L. (Malvaceae)	bark	aqueous	HEp-2	(Lindamulage & Soysa, 2016)
Bhesa ceylanica Thw. (Celastraceae)	leaf/bark	hexane, $CHCl_3$,EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Calophyllum calaba L. (Clusiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Calophyllum moonii Wight. (Clusiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Calophyllum tomentosum Wight (Clusiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Chaetocarpus coriaceus Rich. (Euphorbiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Cocos nucifera L. (Arecaceae)	inflorescence	acetone/water (7:3)	HeLa cells (cervical cancer), PC3 cells (prostate cancer)	(Padumadasa et al., 2016)
Connarus championii Thw. (Connaraceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Campnosperma zeylanica Thw. (Anacardiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Cleistocalyx nervosum Var. (Myrtaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Doona macrophylla Thw. (Dipterocarpaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Gardenia crameri Tirveng. (Rubiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Flueggea leucopyrus (Willd.) (Phyllanthaceae)	aerial parts	aqueous	MCF-7, MDA-MB-231, SKBR-3, MCF-10A	(Mendis, Thabrew, Samarakoon, & Tennekoon, 2015)
	leaf	aqueous	Hep-2 cell	(Soysa, De Silva, & Wijayabandara, 2014)
Lijndenia capitellata (Arn.) K.Bremer (Melastomaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Mangifera zeylanica Hook.f. (Anacardiaceae)	bark	quercetin and catechin, 5-((8Z, 11Z, 14Z)-hexatriaconta-8, 11, 14-trienyl) benzene-1,3-diol	MDA-MB-231, MCF-7, SKOV-3, MCF-10A	(Ediriweera et al., 2016; Ediriweera et al., 2017)
Memecylon rostratum Thw. (Melastomaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Nepenthes distillatorya L. (Nepenthaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Ochna jabotapita L. (Nepenthaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Schumacheria castaneifolia L. (Dilleniaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
	NM	Triterpenoid saponin (3-O-α-L-arabinosyl oleanolic acid)	NCI-H292 lung cancer cells, MRC-5	(Samarakoon et al., 2017)

Name of the plant	*Part of the plant*	*Extract*	*Cell line*	*Reference*
Semecarpus subpeltata Thw. (Anacardiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Thespesia populnea L. (Malvaceae)	bark	aqueous	HEp-2	(Lindamulage & Soysa, 2016)
Vateria copallifera (Retz.) Alston (Dipterocarpaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
	bark	vateriferol	PC12 cells	(Samaradivakara et al., 2018)
Vernonia zeylanica (L.) Less (Malvaceae)	NM	vernolactone	NTERA-2	(Abeysinghe et al., 2019)
Wendlandia bicuspidate (L.) (Rubiaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Wrightia zeylanica (L.) R.Br. (Apocynaceae)	leaf/bark	hexane, $CHCl_3$, EtOAc, MeOH	MCF-7, MDA-MB-231	(Jayarathna et al., 2016)
Medicinal plants used for the management of diabetes mellitus				
Costus speciosus (Koen ex.Retz.) (Costaceae)	leaf	MeOH	Vero cells (monkey kidney cell line)	(Samarakoon et al., 2014)
Cynometra cauliflora L. (Fabaceae)	leaf	EtOH	RAW 264.7 (Murine macrophage)	(Perera et al., 2016)
Murraya koenigii L. (Rutaceaea)	leaf	EtOH	RAW 264.7 (Murine macrophage)	(Perera et al., 2016)
Psidium guajava L. (Myrtaceae)	leaf	EtOH	RAW 264.7 (Murine macrophage)	(Perera et al., 2016)
Spondias dulcis L. (Anacardiaceae)	leaf	EtOH	RAW 264.7 (Murine macrophage)	(Perera et al., 2016)

NM, not mentioned; $CHCl_3$, chloroform; EtOAc, ethyl acetate; MeOH, methanol; EtOH, ethanol; MCF-7, estrogen receptor positive breast cancer; MDA-MB-231, triple negative breast cancer cells; HEp-2, human larynx epithelioma cancer cell lines; SKBR-3, breast cancer cell lines; MCF-10A, non-cancerous breast cell line; SKOV-3, ovarian epithelial cancer; NCI-H292, non-small-cell lung cancer cells; MRC-5, normal lung cells; PC12, pheochromocytoma cells (commonly used as a model for neuroprotection); NTERA-2: human embryonal carcinoma cells; RAW 264.7, murine macrophage cell line

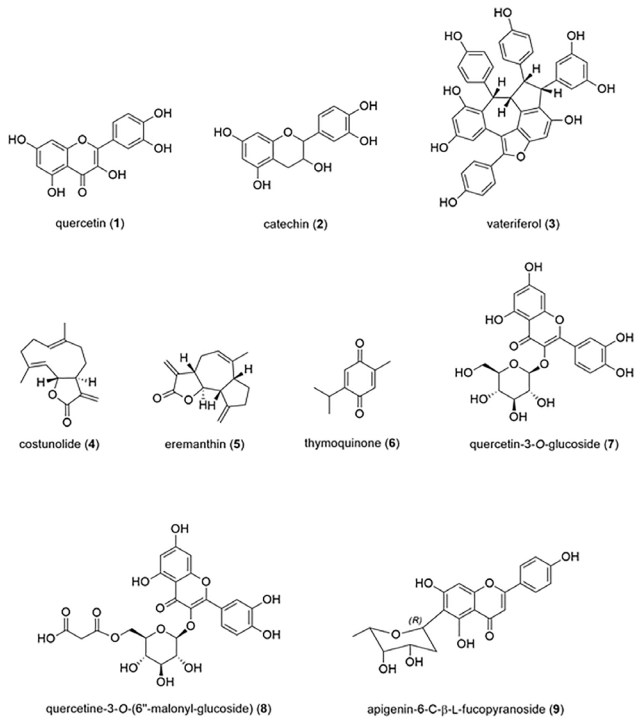

Fig. 4. Structures of metabolites isolated from *M. zeylanica* (1 and 2), *V. copallifera* (3), *C. specious* (4 and 5), *N. sativa* (6), *M. oleifer* (7 and 8) and *A. carambola*[9]

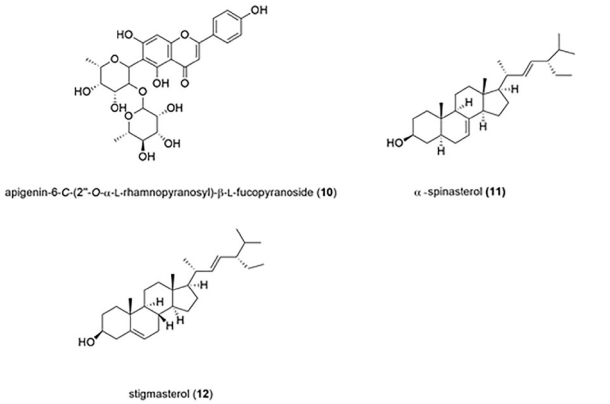

Fig. 5: Structures of metabolites isolated from *A. carambola* (10), *A. sessilis* (11 and 12)

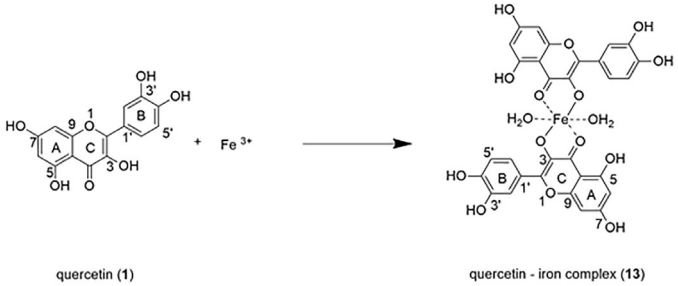

Fig. 6: Conversion of quercetin (1) to the quercetin-iron complex[13]

59.75 ± 1.04%, low grown; 59.47 ± 0.73 %) (Abeywickrama, Ratnasooriya, & Amarakoon, 2011).

DISCUSSION

Many epidemiological studies on medicinal flora have been subjected to determine antioxidant activity. However, some of them are confined to reporting bioactivities without mentioning specific diseases for which they could be used in treatments. Antioxidants have the ability to counteract free radicals, strengthen the immune system by protecting macromolecules and healthy cells, and thus attribute to the therapeutic effects. For example, the intake of resveratrol leads to trigger antioxidant pathways thus suppressing the oxidative stress (Asaduzzaman Khan, Tania, Zhang, & Chen, 2010). Remarkably, most of the medicinal plants with antioxidant activities have been used as effective remedies against diseases i.e. cancers, diabetes mellitus, kidney diseases etc. (Kasote et al., 2015; Škrovánková, Mišurcová, & Machů, 2012). To elaborate this point, it is vital to report scientific evidence on the antioxidant activity of flora that has been used in the management of diseases. Based on the literature, it is evident that antioxidant activity was reported mostly using *in vitro* assays. This might be due to low cost, ease in conductance, feasibility, etc. (Kasote et al., 2015). Among the compounds isolated from Sri Lankan herbs, quercetin (1) and its derivatives act effectively against free radical formation. Quercetin (1) isolated from *M. zeylanica*, quercetin-3-*O*-glucoside (**7**) from *M. oleifer* and *A. squamosal*, quercetin-3-*O*-(6"- malonyl-glucoside) (8) from *M. oleifer* Fig.4 showed the potential to prevent the formation of free radicals by scavenging and chelation of transition metal ions. The structural arrangement of quercetin (1) owes potent antioxidant activity due to the presence of dihydroxyl groups in the B ring and the 4-oxo group, which can conjugate via a double bond between the 2nd and 3rd carbon, hydroxyl groups in the 3rd and 4th carbon (Fig. 6). Reaction between quercetin (1) and free radical is initiated with the donation of an electron and followed by formation of free radical. However, the resulting quercetin radical is likely to be less reactive due to the formation of resonance structures (Mariani et al., 2008). Furthermore, quercetin exhibits potent antioxidant activity with the formation of the quercetin-iron complex (13) as shown in Fig. 6. The combination of transition metal ions such as iron, copper, cadmium, etc. with quercetin enhances the reducibility. This improved antioxidant ability of quercetin (1) is via enabling the prevention or delaying of formation of free radicals (Bodini, Copia, Tapia, Leighton, & Herrera, 1999; Xu, Hu, Wang, & Cui, 2019).

Assessment of antioxidant activity of natural products can be classified into three, based on their activation mechanisms in *in vitro* assays. The hydrogen atom transfer (HAT) mechanism is one of the mechanisms which measures the capability of hydrogen donation to produce stable compounds. Oxygen radical absorbance capacity (ORAC), total radical trapping antioxidant parameter (TRAP), and oxidative radical absorbance capacity (ORAC) assays can be classified under the HAT mechanism. Samaradivakara et al. (2018) evaluated the antioxidant activity in *Vateria copallifera* (Retz.) Alston using ORAC assay. The assay was performed on hexane, EtOAc, EtOH extracts of *Vateria copallifera* (Retz.) Alston bark (Samaradivakara et al., 2018). Based on the inclusion criteria, assessment of antioxidant activity for medicinal plant extracts via TRAP assay was not reported in the present review. Antioxidants with an ability to transfer single electron for reduction of any compound can be identified under the electron transfer mechanism (ET). Ferric reducing antioxidant power (FRAP) and thiobarbituric assay (TBA) are activated following the ET mechanism. *Vernonia cinerea* L. (hexane, chloroform, (EtOAc, aqueous fractions of whole plant and aerial parts, in separate) and *Gracilaria edulis* (Gmel.) Silva. (MeOH, $CHCl_3$, EtOAc, aqueous extracts of the whole plant) were subjected to the FRAP assay to determine antioxidant activity (Gunathilaka, Samarakoon, Ranasinghe, & Peiris, 2019; Navodani et al., 2019). Ethanolic and aqueous extracts of aerial parts of *Trichosanthes cucumerina* L. were evaluated by assessing antioxidant activity using the TBA assay (Arawwawala et al., 2011). Despite these two methods, it could be a combination of both HAT and ET i.e. DPPH and ABTS assays (Apak, 2019; Gupta, 2015; Kasote et al., 2015; Miguel, 2010; Moharram & Youssef, 2014; Pisoschi, Pop, Cimpeanu, & Predoi, 2016). Sri Lankan medicinal plants such as *Gracilaria edulis* (Gmel.) Silva. (MeOH, hexane, $CHCl_3$, EtOAc, aqueous extracts of whole plant), *Syzygium caryophyllatum* (Linn.) Als. (EtOAc, aqueous, and hexane extracts of leaf and fruit), *Abelmoschus moschatus* Medik. (aqueous extract of leaf), *Asparagus falcatus* L. (aqueous extract of leaf) and *Barleria prionitis* Linn. (aqueous extract of the whole plant) were subjected to DPPH and ABTS assays to evaluate antioxidant activity (Amarasiri et al., 2020; Gunathilaka et al., 2019; Wathsara, Weeratunge, Mubarak, Godakumbura, & Ranasinghe, 2020).

Each assay has specific mechanism/s and different antioxidant assays to provide different information based on their reaction mechanisms. In addition, the utilization of free radicals depends on experimental conditions like reagent pH, solubility, and temperature. Therefore, evaluation of antioxidant activity using different assays is essential to obtain a vivid idea of total antioxidant status without restricting to a single assay (Apak, 2019; Pisoschi et al., 2016). Most of the investigations reported screening of crude extract, fractions, and pure compounds using DPPH assay. The screening was performed on ABTS, ORAC, FRAP, NO, and ferrous ion chelating (FIC) assays. The reported IC_{50} values varied depending on the defined procedure, environmental conditions and reagent concentrations etc. (Galketiya, Weerarathna, Punchihewa, Wickramaratne, & Wickramaratne, 2017; Samarakoon et al., 2014; Wathsara et al., 2020). It is worth mentioning that most of the *in vitro* studies were conducted for extracts prepared under different methods, solvents, and mixtures of solvents. The use of different solvents allows plant extracts to extract different phytochemicals according to their polarity and act differently depending on their solubility (Gunathilaka et al., 2019; Jayarathna et al., 2016; Samaradivakara et al., 2018; Samarakoon et al., 2014).

The evaluation of *in vivo* antioxidant activity of natural products was carried out using antioxidant enzyme activities (reduced glutathione, GPx, glutathione-S-transferase, glutathione reductase), and lipid peroxidation (Alam et al., 2013; Attanayake, Jayatilaka, Pathirana, & Mudduwa, 2015b). Oxidative stress is signified by low activity of antioxidant enzymes as a consequence of antioxidant imbalance. In addition, cellular damage due to the ROS and RNS induce the leakage of liver enzymes to the circulation. These elevated

levels of enzymes are evaluated *in vivo* to determine antioxidant activities. The estimation of products of lipid peroxidation is another method to evaluate antioxidant activity. The end product malondialdehyde that forms during the lipid peroxidation process can be used to assess antioxidant activity (Alam et al., 2013; Samuagam, Sia, Akowuah, Okechukwu, & Yim, 2015). However, it is notable that there is a paucity of *in vivo* evidence on antioxidant activity of Sri Lankan plants that have been used for the treatment of diabetes mellitus, cancer, and kidney diseases.

Although several research articles have been published on the antioxidant activity of Sri Lankan flora, there is no single review that describes the antioxidant activity of medicinal flora that is used in oxidative stress-related diseases in detail using *in vivo* and *in vitro* studies. Therefore, we believe the present systematic review would fulfill the gap in literature on antioxidant activity of Sri Lankan herbs which have been used to manage the oxidative stress related diseases. Further investigations are required for the selected extracts, fractions and compounds extensively via *in vivo* pre-clinical studies followed by clinical trials in order to identify potential remedies with scientifically proven bioactivities to reduce or inhibit cellular oxidative stress.

CONCLUSION

The present review describes the reported antioxidant activities of crude herbal extracts, fractions, and pure compounds. Many *in vitro* studies were conducted to evaluate the antioxidant activities of Sri Lankan plants. Among the *in vitro* assays, the DPPH assay is the most reported assay for the evaluation of antioxidant activity, while the ABTS, ORAC, FRAP, NO and FIC assays were also used to evaluate antioxidant activities. However, due to various mechanisms in the principles of the assay, it is worth performing more than one assay to obtain a full insight into the antioxidant potentials. Phytoconstituents such as phenols, kaempferol, coumarins, tannins, anthocyanins, saponins, etc. exert powerful antioxidant activities that can play a vital role in oxidative stress related diseases. Antioxidants are attributed to scavenging free radicals, chain breaking reactions, and chelation of metal ions via diverse mechanisms in order to reduce the damage of macromolecules and other deleterious effects. It is worth to mention that, there is limited evidence about *in vivo* and cell-based studies. However, the information in this review would be useful for further in-depth studies on plant-derived antioxidants that may be conducive to oxidative stress-related diseases.

Compliance with Ethical Standards statements

Not Applicable

Source of Funding

The present review was written as a co-activity in the project which has been financially supported by World Bank under Accelerating Higher Education Expansion and Development-AHEAD (AHEAD/DOR STEM-15), Sri Lanka.

Informed Consent

Not Applicable

Authorship Contributions

Walimuni Nayomi Deshani De Silva: Writing of original draft, Data curation. Pabasara Kalansuriya: Conceptualization, Review and editing, Supervision. Anoja Priyadarshani Attanayake: Supervision, Conceptualization, Writing - review and editing, Data curation, Visualization. Liyanage Dona Ashanti Menuka Arawwawala: Review and editing, Supervision.

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