Antioxidant and enzyme inhibitory activities of selected medicinal plants and chemical characterization of phytoceuticals of *Artocarpus nobilis* and its topical applications

A thesis submitted to Degree of Doctor of philosophy

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November 2019

ABSTRACT

The search for natural cosmeceuticals has gained an increasing demand due to its fewer side effects and become more prevalent in cosmetic formulations. Plant sources contain numerous natural compounds which can be used as whitening, anti-aging anti-wrinkle, antioxidant, anti-inflammatory ingredients and also for the treatment of dermatological disorders. The objective of this study was to determine *in vitro* bioactive properties of selected medicinal plants and to isolate and characterize bioactive compounds and use those as natural bioactive ingredients to develop cosmetic products. Ethanol extracts of 15 selected Sri Lankan medicinal plants were investigated for tyrosinase, elastase, hyaluronidase, arachidonate-5-liposygenase (A5-LOX), xanthine oxidase (XO), acetylcholine esterase (AChE), butylcholinesterase (BChE), α-glucosidase, dipeptidyl peptidase-4 (DPP-4), α-amylase enzyme inhibitory, anti-glycation and antioxidant (2,2-Diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging, Ferric iron reducing antioxidant power (FRAP) and Oxygen radical absorbance capacity (ORAC)) activities and total phenolic and total flavonoid contents using *in vitro* bioassay models.

Bark extract of *Eleocarpus serratus* showed highest elastase inhibitory activity and antioxidant activities and rhizome extract of *Curcuma aromatica* exhibited marked elastase and hyaluronidase inhibitory activities. Bark and leaf extracts of *Artocarpus nobilis*, *A. heterophyllys* and *A. altilis* showed promising tyrosinase, hyaluronidase, A-5-LOX, AChE, BChE enzyme inhibitory and antioxidant activities. Based on these bioactivity results bark extract of endemic species *A. nobilis* was selected for further chemical and biological investigation of their chemical constituents. Further a fairness cream, fairness gel and hand sanitizing gel was prepared incorporating active plant extracts of *A. nobilis*, *A. altilis* and *C. aromatica,* respectively.

Sequential ethyl acetate and ethanol bark extracts of *A. nobilis* were subjected to bioassay-guided fractionation and isolation of compounds which were then characterized by spectroscopic techniques including NMR (^{1}H, ^{13}C, APT, ^{1}H-^{1}H COSY, HSQC, and HMBC), MASS, IR, and UV. The isolated compounds (1, 3 and 4) were evaluated for DPPH free radical scavenging activity, tyrosinase, elastase, hyaluronidase, AChE, BChE, A5-LOX and XO enzyme inhibitory activities and cytotoxicity against three cancer cell lines (HeLa, HCT 116, MCF7), neuroprotection potential by H_2O_2-induced apoptotic cell death of SH-SY5Y cells, and nitric oxide (NO) levels in lipopolysaccharie-induced NO production in SIM-A9

microglial cells. DNA barcoding of *A. nobilis* was carried out for species identification and the sequences were deposited in the Gen Bank.

Two novel compounds, compound 2 and Artolankanin A (compound 3) were identified from the sequential ethyl acetate and ethanol extracts of stem bark of *A. nobilis* along with the known compounds, Artonin E (compound 1) and Artobiloxanthone (compound 4).

Artonin E (compound 1) exhibited marked tyrosinase, AChE, BChE and A5-LOX enzyme inhibitory activities and cell cytotoxicity activity against cancer cell lines HeLa, MCF 7 and HCT 116 and NO inhibition activity in LPS-stimulated microglia cells. Artolankanin A (compound 3) exhibited good A5-LOX enzyme inhibitory activity and cell cytotoxicity activity against cancer cell line HCT 116. Artobiloxanthone (compound 4) exhibited good A5-LOX and AChE inhibitory activities and cell cytotoxicity against HeLa cancer cell line. However, all tested compounds exhibited lower or no biological activity against elastase, hyaluronidase and XO inhibitory activities.

This is the first report of the isolation of two novel compounds, compound 2 and Artolankanin A (compound 3) and known compounds Artonin E (compound 1) and Artobiloxanthone (compound 4) from the stem bark of *A. nobilis* to the best of our knowledge. Furthermore, this is the first report of tyrosinase, elastase, hyaluronidase, AChE and BChE inhibitory activity of these compounds.

The bioactivities, exhibited by these compounds reflect the use of those compounds and its extracts as active agents in cosmeceuticals which may use to treat various skin disorders such as hyper-pigmentation, to obtain lighter skin complexion and for prevent wrinkles and pre-mature aging. The standardized cosmetic products, fairness cream, fairness gel and hand sanitizing gel formulated using extracts of *A. nobilis, A. altilis* and *C. aromatica* could be developed as herbal cosmetics for the cosmetics industry in Sri Lanka. These findings may provide some guidance for the cosmetic industry to design and synthesize potential multi target cosmeceuticals.