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Exploiting the SuperPred Tool for Target Deconvolution of Novel Bioactivities of Drug-Like Phytomolecules from Aglaia Species

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INTRODUCTION & AIM

Ever since the isolation of aglaiol, a dammarane-type triterpenoid from Aglaia species in the mid-1960s, several other molecules have been isolated from the leaves, root, stembark and seeds of various species. Some of the isolated molecules were screened and found to possess antiviral, cytotoxicity, antituberculosis, insecticidal, molluscidal anti-inflammatory and antifungal activities. A significant number of the isolated molecules have not been tested for any biological activities, hence the need for prospective study while those already screened for activities may have limited phenotypic targets, are under-utilized or may require retrospective validation.

Drug-target interaction or drug-fishing prediction has revolutionized drug discovery by its potential to identify target for phenotypic screening hits or polypharmacology of molecules already having some known targets as well as unintended off-targets of those molecules. The SuperPred has shown robustness in both prospective and retrospective target deconvolution studies. In this study, 386 molecules previously characterized from Aglaia species were subjected to drug-likeness predictions using Lipinski's rule of five (Ro5) and those that passed were subjected to target deconvolution using SuperPred web tool for both prospective and retrospective target identification.

METHOD

A total of 386 secondary metabolites reported from the genus Aglaia as at June 2024 were obtained from extensive review of literature. Before the compilation, the nomenclature of the Aglaia species was confirmed at https://www.theplantlists.org. The drug-likeness properties of the collected secondary metabolites were predicted using SwissADME web tool based on Veber (rotatable bonds, RTB $\leq$ 10 and topological polar surface area, TPSA $\leq$ 140), Egan (WLOGP $\leq$ 5.88 and TPSA $\leq$ 131.6), Muegge (200 $\leq$ MW $\leq$ 600, -2 $\leq$ XLOGP $\leq$ 5, TPSA $\leq$ 150, HBDs $\leq$ 5 and HBAs $\leq$ 10), Ghose (60 $\leq$ MW $\leq$ 480, 40 $\leq$ MR $\leq$ 130, -0.4 $\leq$ WLOGP $\leq$ 5.6, and 20 $\leq$ atoms $\leq$ 70) and Lipinski (MW $\leq$ 500, HBAs $\leq$ 10, HBDs $\leq$ 5, logP(o/w) $\leq$ 5, and RTBs $\leq$ 5) algorithmic rules.

The canonical SMILES string of a compound was loaded on the SuperPred3 ChemDoodle web interface which predicted the anatomical therapeutic chemical (ATC) class and target by logistic regression machine learning models, based on Morgan fingerprints of length 2048. In each run, the ATC codes, representing five levels (anatomical, therapeutic, therapeutic/ pharmacological, chemical/ therapeutic/ pharmacological and chemical substance) was assigned. The ChEMBL data base was used for data filtration of the targets while the accuracy of the machine learning models for target prediction performance was validated by leave-one-out 10-fold cross validation. The model performance was evaluated by probability and accuracy scores. The probability score defined the probability that the input structure binds with the specific target as determined by the respective target machine learning model

RESULTS & DISCUSSION

The phytochemical composition of the genus Aglaia provides important molecules with potential to be developed into therapeutic agents for the treatment of various diseases. Diverse phytoconstituents such as alkaloids, terpenoids, flavonoids, saponins, tannins have been isolated and characterized from different morphological parts of the species of the genus Aglaia (Table 1).

Phytochemical	No of compounds
Flavaglines	123
Triterpenoids	107
Sesquiterpenoids	33
Diterpenoids	5
Limonoids	22
Steroids	55
Alkaloids	29
Lignans	12

The study identified G-protein coupled receptor 55, DNA-(apurinic or apyrimidinic site) lyase, indoleamine 2,3-dioxygenase, dual specificity protein kinase, nuclear factor NF-kappa-B p105 subunit, cathepsin D, cannabinoid CB2 receptor, MAP kinase ERK2, cyclooxygenase-1, tyrosyl-DNA phosphodiesterase 1, bloom syndrome protein, endoplasmic reticulum-associated amyloid β-protein, eukaryotic initiation factor 4A-I, hypoxia-inducible factor 1-α, dipeptidyl peptidase IV, indoleamine 2,3-dioxygenase, thrombin, transcription intermediary factor α, HERG, Niemann-Pick C1 protein, mineralocorticoid receptor, arachidonate 12-lipoxygenase as potential targets for the Aglaia compounds.

These targets were also identified to encode for the diseases and indications such as attention deficit hyperactivity disorder, melanoma, glioma, ocular cancer, solid tumour/cancer, acute myeloid leukaemia. glioma, immune response, homeostasis and inflammation, multiple sclerosis, hypertension, management and treatment of appetite/weight loss from HIV/AIDS and chemotherapy in addition to epilepsy, regulate cell proliferation, cell differentiation, cell death in eukaryotes from yeast to humans, analgesic, anti-inflammatory, anti-pyretic, cancer, severe prenatal and post-natal growth of deficiencies, sensitivity to sunlight, insulin resistance, and high risk to many cancers that occur at an early stage, Alzheimer disease, prevent replication of various, divergent RNA viruses, cancer, diabetes, obesity, Alzheimer's disease, Parkinson disease, promotes the efficacy of immune check, point blockade in the treatment of non-small cell lung cancer, type 2 diabetes mellitus in adult, acute myeloid leukaemia, b-cell lymphoma, brain and colorectal cancer, depression, gastric adenocarcinoma, glioma, head and neck cancer, melanoma, pancreatic cancer, prostate cancer, angina pectoris, asthma, atopic dermatitis, bleeding disorder, tissue injury, immune responses, fibrosis, cancer, neurodegenerative disease, cardiac safety, anti-arrhythmic, therapies, epilepsy, schizophrenia, regulates cholesterol, cancer, Alzheimer disease, Parkinson disease, infectious diseases, hypertension, heart failure, atrial fibrillation, pulmonary, hypertension, renal failure, stroke, anti-inflammatory role in asthma airway inflammation

CONCLUSION

The findings of this study underscore the therapeutic potential of phytochemicals from Aglaia species, highlighting their potential as sources of effective and safe treatments for various diseases. The predicted interactions with biological targets in cancer, inflammation, and microbial infections provide a foundational understanding that supports traditional medicinal uses of Aglaia species.

FUTURE WORK / REFERENCES

Experimental validation through in vitro and in vivo studies is necessary to confirm the predicted therapeutic efficacy and safety of these compounds

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