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Drug likeliness, pharmacokinetics profiling and efficacy of *Polyscias fulva* bioactive compounds in the management of uterine fibroids; An integrative *in silico* and *in vivo* approach

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Highlights

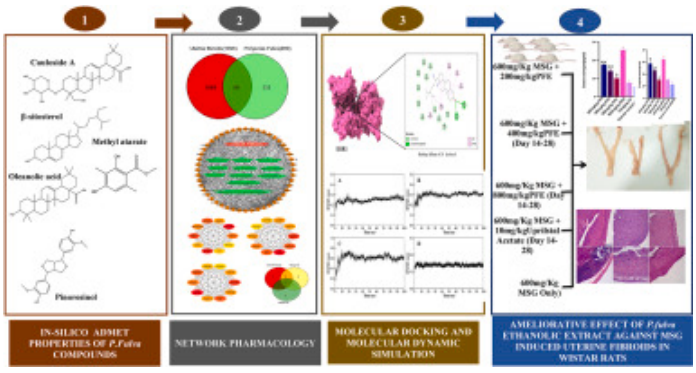
- Four compounds—pinoresinol, lichexanthone, methyl atarate, and β-sitosterol—exhibited drug-likeness properties with moderate safety profiles.
- A total of 48 uterine fibroid targets were identified, with key targets being HIF1A, ESR1, EGFR, and CASP3.
- β-sitosterol exhibited the strongest binding affinities, particularly with EGFR (−9.75 kcal/mol) and HIF1A (−9.21 kcal/mol).
- MD simulations confirmed high stability of protein-ligand complexes, with CASP3 showing the lowest deviation (RMSD 0.14 nm).
- In Wistar rats, *Polyscias fulva* ethanolic extract reduced serum proteins, cholesterol, estrogen, and progesterone levels and preserved uterine histoachitecture against MSG-induced uterine fibroid**s.**

Abstract

Polyscias fulva is traditionally used in Uganda for the management of Uterine fibroids (UF). However, there is paucity of data regarding its efficacy, biological targets and potential mechanisms of action hence prompting scientific validation process through insilico and invivo approaches. In this study, we utilized network pharmacology, molecular docking, molecular dynamic simulations and invivo assays to investigate the drug likeliness, pharmacokinetics and efficacy of *Polyscias fulva* against Uterine fibroids.

Four *Polyscias fulva* bioactive compounds; pinoresinol, lichexanthone, methyl atarate, β-sitosterol exhibited drug likeness properties with moderate safety profiles. Forty-eight (48) uterine fibroid targets were identified as potential targets for the eleven *Polyscias fulva compounds*. Protein-protein interaction (PPI) analysis revealed four key targets (HIF1A, ESR1, EGFR, and CASP3). The KEGG pathway and GO enrichment analyses revealed that these key targets play significant roles in regulating the positive regulation of cyclin-dependent protein serine/threonine kinase activity, positive regulation of nitric-oxide synthase activity and positive regulation of transcription, DNA-templated. β-sitosterol demonstrated the strongest binding affinity with the four targets, showing particularly strong affinities for EGFR (−9.75 kcal/mol) and HIF1A (−9.21 kcal/mol). Molecular dynamics (MD) simulations revealed high stability in these protein-ligand complexes, with CASP3 displaying the lowest deviation and most consistent RMSD (0.14 nm) of the protein, followed by EGFR (0.25), HIF1A (0.29), and ESR1 (0.79). In-vivo evaluation on female Wistar rats with *Polyscias fulva* ethanolic extract showed an ameliorative effect of the extracts against monosodium glutamate-induced (MSG) UF. Treated animals exhibited a decrease in serum proteins, cholesterol, estrogen, and progesterone levels ($P<0.05$) and the extract preserved uterine tissue histoachitecture as compared to controls. In conclusion, *Polyscias fulva* demonstrates potential ameliorative activity against UF with promising pharmacokinetic properties and safety profiles.

Graphical abstract



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Introduction

Uterine leiomyomas (fibroids) are the most common pelvic tumors among women of reproductive age, affecting more than 70% of women worldwide [1]. Several factors contribute to the growth and

progression of fibroids, including; genetic, biological, and hormonal factors [2]. Leiomyomas are often associated with several gynaecological problems such as dysmenorrhea, irregular pelvic pain and menorrhagia [3]. The black women population has a higher prevalence of fibroids (18.5%) than other racial/ethnic groups [1,4]. The estrogen signaling pathway is a key driver pathway in uterine fibroid development and comprises both genomic (direct and indirect effects of gene expression) and non-genomic factors, such as; the Ras-Raf-MEK (MAPK/ERK kinase)-mitogen-activated protein kinase (MAPK), PI3K-phosphatidylinositol-3,4,5-trisphosphate (PIP3)-AktmTOR) pathways, Ras-Raf-MEK-MAPK and PI3KPIP3-Akt-mTOR pathways, respectively [5,6] Alterations in other critical pathways such as the WNT/β-catenin, TGF-β, growth factor–regulated signaling, ECM, YAP/TAZ, Rho/ROCK, and DNA damage repair pathways also play essential roles in uterine fibroids formation and development [5]. Notably, the development of uterine fibroids may be initiated and triggered by the interactions and crosstalk among these pathways.

Surgical procedures such as hysterectomy, myomectomy, uterine artery embolization (UAE) and magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS) are recognized as the most definitive therapeutic interventions. However, the possibility of recurrence due to underlying risk factors exists [7,8]. Pharmacologically, non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, and naproxen) [9], gonadotropin-releasing hormone analogs (leuprolide acetate, cetrorelix), synthetic antiprogestin steroids (mifepristone and asoprisnil), aromatase inhibitors, and selective progesterone receptor modulators (SPRMs) are currently used in management/treatment of UL [10,11]. However, these drugs are associated with several adverse effects, short alleviation of symptoms, non-curative, and often many patients ultimately go for surgical alternatives, which are also associated with operative mortality and morbidity [12,13].

Polyscias fulva is one of the medicinal plants traditionally used in East and Central Africa in the management of uterine fibroids, cancer and other related conditions [14]. The therapeutic effects of *P. fulva* are thought to arise from various biologically active compounds. phytochemical studies performed on *P. fulva* stem bark yielded eleven (11) compounds [15]. Six compounds were isolated from the ethyl acetate fraction and five from the n-butanol fraction. The compounds belonged to various chemical groups, but commonly saponins and triterpenoids [16]. Unlike conventional medicines, herbal medicines are multi-target and multi-component recipes whose bioactive components interact and modulate complex molecular and biological networks within the body to produce their specific therapeutic or toxic effects [17,18]. Thus, understanding the complex nature of how herbal medicines work is a challenge of every drug development programme. Novel and robust approaches to systematically investigate the pharmacokinetics, pharmacodynamics, and safety of herbal remedies are required [19].

Recent approaches emphasize the use of computer aided drug discovery (CAAD) to shorten the drug discovery process, and reduce cost of production [20] as opposed to the traditional drug design and development approaches, which are complex, time consuming, and costly [21]. Network pharmacology in conjunction with other several bioinformatic databases aid the expeditious establishment of relationships between drug-target-disease networks and associated pathways [22]. The above advances coupled with molecular docking approaches that provide insight into the molecular interactions between ligands and targets at specific binding sites have enabled scientists to gain a detailed understanding of the specific interactions between bio-active compounds and

genes associated with various diseases, thus accelerating the development of potential therapeutic interventions [23]. In this study, we employed the network pharmacology approach, molecular docking, molecular dynamic simulations and invivo experimental approaches to explore the pharmacokinetics, safety, efficacy and mechanism of action of *Polyscias fulva* bioactive compounds in the management of uterine fibroids.

Section snippets

Bioactive compounds identification

A Scholarly Literature search for the identification of the bioactive compounds *Polyscias fulva* was conducted from literature repositories such as PubMed (https://pubmed.ncbi.nlm.nih.gov ↗ ,accessed on 28th/October/2023), Springer (https://link.springer.com ↗, accessed on 28th/October/2023) and Science Direct (https://www.sciencedirect.com ↗, accessed on 28th/October/2023). …

Drug-likeness prediction, pharmacokinetics and toxicity screening of *Polyscias fulva* bioactive compounds

The *Insilico* screening methods were applied to evaluate the drug likeliness (DL) features and the pharmacokinetic parameters i.e. …

Collection and preparation of plant materials

Polyscias fulva stem barks were collected from Mabira forest, Buikwe district Central Uganda (0°24′11.6″N 33°00′22.6″E) in June 2023. Good harvesting and conservation practices were followed under guidance of a plant taxonomist. For references purposes, we prepared a voucher specimen and deposited it at the Makerere University Herbarium, at the Department of Plant Sciences, Microbiology & Biotechnology. The stem barks were carefully packed in zip lock bags and transported to the laboratory at …

Identified bioactive compounds of *P. fulva*

From the literature search, we retrieved eleven reported bioactive compounds of *P. fulva* with scientifically validated pharmacological activities; 3-O-[α-L-arabinopyranosyl]-hederagenin (cauloside A) [37], Beta-Sitosterol [38], Kalopanaxsaponin B [15,37], Lichexanthone [37], Methyl

atarate (Methyl 2,4-dihydroxy-3,6-dimethylbenzoate) [16,37], Oleanolic acid [16], Pinoresinol [38], Polyscioside A [37], Quercetin-3-O-D-glucopyranoside, Sequalene and α-hederin [39]. …

Drug-likeness, pharmacokinetics and toxicity profile of the retrieved bioactive compounds of *P. fulva*

The SwissADME screening results (…

Discussion

The current therapeutic options for the management of uterine fibroids come with several limitations necessitating the search for alternative options that are not only affordable and effective but also safe for the patient. In this study we investigated the safety, pharmacokinetics and mechanism of action of *P. fulva* bioactive compounds in the management of uterine fibroids using computer aided drug discovery approaches and in-vivo validation. The therapeutic efficacy of plant's bioactive …

Conclusion

In conclusion, this study provides compelling evidence for the therapeutic potential of *P. fulva* in uterine fibroid management. However, these investigations were conducted primarily through in-silico and in-vivo methods, to translate these findings into clinical application, future research should focus on metabolomics profiling, dose optimization, toxicity profiling, regulatory compliance, and clinical validation. Addressing these challenges will pave the way for the development of *P. fulva* …

CRediT authorship contribution statement

Kenedy Kiyimba: Writing – review & editing, Writing – original draft, Software, Resources, Formal analysis, Data curation, Conceptualization. **Lincoln Munyendo:** Writing – review & editing, Supervision, Formal analysis, Data curation, Conceptualization. **Samuel Baker Obakiro:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Yahaya Gavamukulya:** Writing – review & editing, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Ayaz Ahmed:** …

Data availability

All data is available in the manuscript. …

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Declaration of competing interest

We have nothing to declare. …

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