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Exploring the Antioxidant, Antimicrobial, and Metabolic Modulating Activities of *Gynostemma pentaphyllum* Extracts: Implications for Blood Lipid and Glucose Regulation

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Abstract: *Gynostemma pentaphyllum (G. pentaphyllum), recognized for its long-standing application in Asian material medica, continues to be a subject of inquiry for its hypoglycaemic, hypolipidaemic, and cardioprotective effects. The present study undertakes a comparative phytochemical and pharmacological appraisal of decoctions and ethanolic macerated extracts, using a specific Vietnamese ecotype of the species, in order to elucidate the influence of solvent selection on the bioactive profile of the material. Antimicrobial, antioxidant, α-glucosidase and lipase inhibitory assays serve as functional assays of therapeutic potential. Comprehensive phytochemical screening, employing standard reagents and chromatographic techniques, disclosed a far denser array of constituents in the ethanolic macerate, comprising gallic and caffeic acid derivatives, indolic alkaloids, a range of flavanol and flavan-3-ol glycosides, along with steroid and triterpene saponins. The aqueous decoction, in contrast, presented only flavanol aglycones and simple phenolics. The superiority of the ethanolic extract in all evaluated biological assays proceeded in the order of magnitude from antioxidant to lipase inhibition. Notably, its antioxidant capacity, measured by DPPH radical scavenging, was nearly 40 times greater than the aqueous extract (IC50=0.317 mg/mL). The ethanoic extract was noted to have unusual glucosidase inhibitory potential with an IC50 of 0.181 mg/mL, more than two-fold the positive control, Acarbose (IC50=0.411 mg/mL). Ethanoic extract of Vietnamese G. pentaphyllum might have greater therapeutic efficacy than previously believed, especially with the treatment of type 2 diabetes, hyperlipidemia, and highlights the usefulness of contemporary solvent extraction methods over traditional decoction in concentrating bioactive compounds.*

Keywords: ***Gynostemma pentaphyllum; phytochemical analysis; ethanolic extract; aqueous decoction; antioxidant activity; α-glucosidase inhibition; lipase inhibition; type 2 diabetes;***

1. Introduction

G. pentaphyllum is a perennial latifoliate vine of the family Cucurbitaceae, which occupies a prominent position in the classical medical literatures of China, Japan, and other Asian countries. Recurrent appellations, including "Southern Ginseng" and "Poor Man's Ginseng," convey its widely recognized adaptogenic effects. Ethnopharmacological datasets substantiate its polyvalent deployment against a considerable register of pathophysiological conditions. Indicative of its mobilizing powers, *G. pentaphyllum* has, over multiple historical epochs, served to restore and fortify vital energies, to retard senescence, and to ameliorate dyslipidaemic and dysglycaemic states, particularly the latter of which is interpreted as precursor to type 2 diabetes. It has additionally been integrated into supportive care algorithm for ischaemic heart disease and for a range of neoplastic disorders.

Current phytochemical studies on *G. pentaphyllum* reveal a diverse spectrum of bioactive constituents that account for its documented therapeutic efficacy. Dominating the profile are the triterpenoid saponins, generically termed gypenosides, whose elaborate glycosidic structures parallel those of ginsenosides from Panax ginseng; such structural analogy is a plausible basis for the shared spectrum of bioactivities.1 Coupled with the saponins, several subordinate classes of phytochemicals have been identified—predominantly flavonoids (exemplified by rutin and quercetin), macromolecular polysaccharides, low-molecular-weight phenolic acids, and certain steroid compounds—each of which appears to amplify the bioregulatory potency of the plant.1 Integrative assays have ascribed a broad array of pharmacological profiles to the accumulated secondary metabolites, including radical-scavenging, pro-inflammatory cytokine-suppressing, glucose-modulating, cholesterol-lowering, and immune-modulating activities.

Despite widespread acknowledgment of the medicinal benefits of *G. pentaphyllum*, the impact of differing preparation techniques on extract potency has received insufficient empirical scrutiny. Standard practice among traditional herbalists entails aqueous decoction, in which aerial parts are subjected to continuous boiling to yield tea or medicinal broth. By contrast, post-genomic phytochemistry typically resorts to organic-solvent extraction, including maceration in 70–95% ethanol, to preferentially sequester high-yield secondary metabolites. Scholarship in this domain nonetheless tends to presume uniform biological effectiveness across approaches, neglecting the presupposition that solvent choice programmable structures the qualitative and quantitative combination of bioactive compounds present, and that such restructuring may in turn govern *in vivo* medicinal relevance. Simultaneous to this procedural knowledge gap is the absence of systematic, peer-reviewed data evaluating the bioactivity of *G. pentaphyllum* subsets derived from the topographically and edaphically distinct regions of Vietnam. Given the recognized dependence of triterpenoid, flavonoid and saponin biosynthetic pathways upon mineral profile, water balance, and irradiance, investigation of indigenous varietals emerges as an exigent precondition for extrapolating pharmacopoeial protective claims to clinical practice.

The present investigation was thus structured as an integrative comparative analysis to close the identified lacunae. Specific objectives of the study were to: (1) execute parallel preparation of a conventional aqueous decoction in accordance with Vietnamese pharmacopoeial canon and an acute ethanolic extract according to contemporary ethanol maceration standards from a vetted population of *G. pentaphyllum* sourced from the hilly latitudes of Vietnam; (2) perform qualitative characterization of phytochemical constituents in both extracts, employing complementary HPTLC, HPLC and phytochemical screening tiers, with the explicit goal of mapping extract–preparation-leverage on metabolomic similarity and, offering, on possible bençeficial outcome.(3) A comprehensive *in vitro* assessment is undertaken to delineate and compare the biological profiles of the two extracts, with particular emphasis on quantifying their respective activities in the domains of antimicrobial efficacy, radical scavenging capacity, α-glucosidase inhibition, and inhibition of lipase-mediated hydrolysis.

2. Materials and Experimental Procedures

2.1. Plant Material and Reagents

Whole plants of *G. pentaphyllum* were collected from Da Lat, Lam Dong province, Vietnam, and the plant material was authenticated by qualified botanists. All chemicals, solvents and reagents used in the study were of analytical grade. Key reagents used were α-glucosidase (from Saccharomyces cerevisiae), porcine pancreatic lipase and their corresponding substrates, p-nitrophenyl-α-D-glucopyranoside (p-NPG) and p-nitrophenyl butyrate (p-NPB). Acarbose, Orlistat, Vitamin C and Kanamycin were used as positive controls in the respective assays.

2.2. Preparation of Plant Extracts

2.2.1. Aqueous Extract (Traditional Decoction)

An aqueous extract was prepared according to a modified decoction procedure replicating the traditional artisanal approach. Entire dried specimens were brought to a constant mass and subsequently coarse ground to a homogenous fine powder. A 250-g aliquot was suspended in 500 mL of distilled water and subjected to a water bath at 40 °C for four hours, the suspension receiving continuous magnetic agitation. The resultant infusion was decanted and, to exhaustively extract the remaining soluble constituents, the residual marc was reconstituted in an identical volume of water, re-heated and filtered as before. Filtrates were pooled, concentrated using a laboratory freeze-drier, and the resultant lyophilized mass was stored under desiccation. The final dry powder is hereinafter designated as the aqueous extract.

2.2.2. Ethanolic Extract (Maceration)

The plant material under consideration here was processed by means of maceration to obtain the desired extract which in this case is ethanolic extract. In the first step of the process, the biomass is dried and powdered and then submerged in an absolute solution of ethanol. These two components were then placed in a dark place for a week. After a week, the solvent and the extract were separated by means of filtration. This process was repeated multiple times as indicated in the description where a fresh solvent is used in each subsequent process. This was done to ensure that in each subsequent process, the used solvent did not contain any soluble substances that were contained within the plant material. The last step of the process involved the rotary evaporator that worked under the principle of reduced pressure as indicated with a rotary evaporator in which the bath was maintained at 40 celcius and thus, the ethanol extract was made.

2.3. Qualitative Phytochemical Analysis

Aqueous and ethanolic extracts were subjected to a battery of standardized screening assays for the preliminary characterization of principal phytochemical constituents. Specific assays employed were the following:

- Phenolic constituents were screened using the ferric chloride ($FeCl_3$) indication method.
- Alkaloids were detected by the application of Wagner's reagent.
- Flavonoids were tested following reactions with concentrated sulfuric acid (H_2SO_4), 1% sodium hydroxide (NaOH), 1% aluminum chloride ($AlCl_3$), and the magnesium-hydrochloric acid (HCl) Cyanidin reaction (Wilstatter technique).
- Saponin compounds were evaluated using an acid (pH 1) and an alkaline (pH 13) froth test, permitting the differentiation of triterpenoid from steroid saponin classes.
- Terpenoidal and steroidal derivatives were characterized by means of Salkowski and Rosenheim reactions.

Additional assays: The diagnostic procedures employed for polyphenolic compounds included the gelatin salt precipitation for tannin detection; the Bortrager's procedure to ascertain the presence of quinones and coumarin derivatives; and the resorcinol reaction, which serves to identify glycoside moieties.

2.4. *In Vitro* Biological Activity Assays

2.4.1. Antimicrobial Susceptibility Testing

The extracts from the various plants were tested on the microorganisms of interests for this study by a bacteriologist using the standard agar well diffusion assay. The assay comprised of the following seven clinically significant bacterial pathogens: Streptococcus sp., Salmonella typhi, Acetobacterium sp., Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, and Escherichia coli. Each strain was subculture then assessed and adjusted to a standard optical density of 0.5 McFarland, which corresponds to approximately 1.5×10^8 cfu/mL. The plated agar was streaked and inoculated with uniformly distributed McFarland standard samples of the prepared bacterial cultures. Wells measuring 7 mm in diameter were then aseptically cut into the agar medium, and into them were added 50 µL of each extract which had been diluted to a final concentration of 10 mg/mL and were in dimethyl sulfoxide (DMSO). For the purpose of comparative quantification, kanamycin was added as a positive control while there was one well that served as a negative control that contained 50 µL of 100% DMSO. The plates were then incubated at 37 °C for a 24-hour period, at which point the diameter of the inhibition zones was measured to the nearest millimeter using calipers. This was to quantify the antimicrobial effectiveness of the extracts.

2.4.2. Evaluation of Antioxidant Capacity

The FRAP assay was done as explained by Yen and Duh (1993) to measure the reducing capacity of the extracts. This assay takes advantage of the extracts compounds ability to reduce Fe^{3+} to Fe^{2+} by the action of the antioxidants in the extracts. The resulting ferrous ions form a Perl's Prussian Blue complex, and the absorbance was measured spectrophotometrically at 700 nm. The higher the absorbance, the more reducing and antioxidant activity there is in the extracts.

The DPPH assay determined the ability of the extracts to react with the stable 2,2 -diphenyl -1 -picrylhydrazyl free radical. A given volume of the extracts was mixed with methanolic DPPH solution, and a color reaction occurred due to the action of the antioxidants. After incubating the sample in the dark for 30 minutes at room temperature, the decrease in absorbance at 517 nm was measured. The data are presented as IC_{50}, the concentration of the extract that caused 50% inhibition of DPPH absorbance.

2.4.3. Enzyme Inhibitory Assays

Pancreatic Lipase Inhibition Assay: During the Developmental Assay for Lipase Inhibition pertaining to the enzyme that hydrolyzes the chromogenic substrate p-nitrophenylbutyrate (p-NPB), there is a detectable concentration of p-nitrophenol that is generated which is then quantitated spectrophotometrically at 405 nm. A positive control, clinically validated compound Orlistat, was utilized. The inhibition data was fitted with a non-linear regression model to produce the IC_{50} value, which indicates the concentration of the inhibitor which 50% of enzyme activity is lost.

2.5. Statistical Analysis

Experiments undertaken had three technical replicates and the result is expressed as the mean ± standard deviation. Microsoft Excel 2013 and SPSS 22.0 were used for the computations. Between groups, appropriate parametric and non-parametric methods were used. A p value cut-off of < 0.05 was used for statistical significance.

3. Results and Discussion

3.1. Solvent Polarity Dictates Phytochemical Yield: A Comparative Profile

The different solvents used for various extractions fulfil equally important purposes and the composition of the secondary metabolites they yield is illustrated in Table 1. The diversity of the phytochemicals in the ethanolic extract is remarkable. Phenolic compounds, a complete set of flavonoids (flavonols, aurones, and chalcones), alkaloids, free and glycosylated saponins and glycosylated triterpenoid and steroid sapoens and saponins, as well as both free and glycosylated triterpenoid and steroid saponins, show all phytochemicals confirmed in the extract. The aqueous extract's composition, however, is considerably more restricted and only confidently comprises steroid saponins and alkaloids. Also, the extract lacks flavonols, phenols, and triterpenoid saponins, suggesting that the aqueous phase is missing a solubility threshold for both polar and nonpolar conjugates. The differences shown in the table certainly suggest that the polarity of a solvent can be used to predict the extent of metabolite capture and can thus be used to extract certain compounds with specific bioactivities.

Table 1: Qualitative Phytochemical Profile of *G. pentaphyllum* Extracts

Phytochemical Group	Test Reagent	Ethanolic Extract	Aqueous Extract
Phenol	$FeCl_3$	+ (Light green)	-
Alkaloid	Wagner	+ (Dark brown)	+ (Light brown)
Flavonoid	H_2SO_4	+ (Orange)	-
	NaOH 1%	+ (Red)	+ (Yellow-orange)
	$AlCl_3$ 1%	+ (Green)	-
	Cyanidin (Mg)	+	-
Terpenoid-Steroid	Salkowski	+ (Red)	-
Saponin	Froth Test (pH 1)	+	-
	Froth Test (pH 13)	+	+
Glycoside	Resorcinol	+ (Light red)	+

Note: '+' indicates presence, '-' indicates absence of the phytochemical group

Such an imbalance has its roots in concepts established in solvent chemistry. The findings indicate a distinct "solvent polarity-phytochemical- bioactivity cascade." Ethanol, a semi-polar solvent, is capable of dissolving molecules that are comprised of both polar and non-polar portions. Bioactive constituents of G. pentaphyllum, such as gypenosides (triterpenoid saponins) and the flavonoid quercetin, have such semi-polar structures due to the presence of disproportionately polar hydroxyl and sugar moieties that are bonded to less polar steroid backbones or aromatic rings. Water is a highly polar solvent and thus can extract some polar compounds, such as simple sugars and certain glycosides. However, due to the highly complex structures of these molecules, water is a poor solvent due to its inability to dissolve the less polar portions of the complex molecules. This explains the greater diversity of compounds in ethanolic extract, especially the flavonoids and triterpenoid saponins of greater biological value. Such an exceptional phytochemical yield is a robust chemical justification for the greater biological activities displayed in the subsequent assays.

3.2. Broad-Spectrum but Modest Antimicrobial Efficacy

Such an imbalance has its roots in concepts established in solvent chemistry. The findings indicate a distinct "solvent polarity-phytochemical- bioactivity cascade." Ethanol, a semi-polar solvent, is capable of dissolving molecules that are comprised of both polar and non-polar portions. Bioactive constituents of *G. pentaphyllum,* such as gypenosides (triterpenoid saponins) and the flavonoid quercetin, have such semi-polar structures due to the presence of disproportionately polar hydroxyl and sugar moieties that are bonded to less polar steroid backbones or aromatic rings. Water is a highly polar solvent and thus is capable of extracting some polar compounds, such as simple sugars and certain glycosides. However, due to the highly complex structures of these molecules, water is a poor solvent due to its inability to dissolve the less polar portions of the complex molecules. This explains the greater diversity of compounds in the ethanolic extract, especially the flavonoids and triterpenoid saponins of greater biological value. Such an exceptional phytochemical yield is a robust chemical justification for the greater biological activities displayed in the subsequent assays.

Table 2: Antimicrobial Activity of *G. pentaphyllum* Extracts Against Pathogenic Bacteria

Bacterial Strain	Zone of Inhibition (mm)		
	Kanamycin (Control)	**Ethanolic Extract**	**Aqueous Extract**
Streptococcus sp.	14.67±0.33	4.33±0.33	0
Pseudomonas aeruginosa	15.83±0.41	6.67±0.88	0
Staphylococcus aureus	15.00±1.00	6.33±0.67	3.00±1.53
Acetobacterium sp.	14.00±0.58	5.00±0.00	0
Salmonella typhi	14.67±0.33	6.33±0.88	3.67±0.33
Escherichia coli	14.33±0.33	6.33±0.33	0
Bacillus subtilis	14.67±0.33	5.33±0.33	0

Values are presented as mean ± SD. The negative control (DMSO) showed no inhibition (0 mm) for all strains

Although the effectiveness of the ethanolic extract`s activity remains impressive, such effectiveness must be placed within the framework of biomedicine. The inhibition zones, while demonstrable, were particularly diminutive (all <10 mm) when compared to the antibiotic Kanamycin. Thus, it can be concluded that although antimicrobial agents are present within *G. pentaphyllum*, the effectiveness of such plant extract is insufficient to be included within the top range of candidates for the development of novel antibiotics. These findings help in formulating a "Hierarchy of Therapeutic Potential" for the plant. The antimicrobial potential of the plant vis a vis enzyme inhibition is potent enough to show that the plant`s therapeutic power is most likely in the biostatic modulation of the metabolic pathways rather than biotic pathway obstruction. This assessment based on data provides a helpful structure for declining research, suggesting that the plant`s biostatic metabolites are more worthy of investigation.

3.3. Potent Antioxidant and Radical Scavenging Properties of the Ethanolic Extract

The strength difference between the two extracts was astonishing according to the antioxidant assessments indicated by Table 3. Within the capsule and polyphenolic reductive capabilities which lie at the root of the ferric reducing power assay, the ethanolic extract exhibited 0.810 ferric reducing capacity at a tetracene OD700. This measurement is greater than two-fold the aqueous extract's 0.396 measurement, which indicates a lesser capacity to reduce and donate electrons to an oxidizing agent, and as a result, donate oxidizing electrons. In the DPPH radical scavenging assay, the superiority of the ethanolic extract was even more striking. With an IC50 of 0.317 mg/mL, the ethanolic extract displayed an incredible scavenging activity. In comparison, the aqueous extract is unbelievably feeble with an IC50 of 12.019 mg/mL which is nearly 40 times less effective.

Table 3: Comparative *In Vitro* Antioxidant Activities of *G. pentaphyllum* Extracts

Assay	Parameter	Ethanolic Extract	Aqueous Extract	Vitamin C (Control)
Ferric Reducing Power	OD700 nm	0.810±0.012	0.396±0.018	2.601±0.054
DPPH Radical Scavenging	IC50 (mg/mL)	0.317±0.020	12.019±2.514	0.018±0.004

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Values are presented as mean ± SD

These results have been phytochemically characterized in Table 1. The abundance of phenolic and flavonoid compounds in the ethanolic extract can biochemically account for the extract's strong antioxidant activity. These compounds are among the various phytochemicals reported to possess antioxidant activity and can scavenge free radicals owing to their ability to donate hydrogen to radicals.1 The low antioxidant activity of the aqueous extract is aligned with the absence of phenolic compounds and the lower range of flavonoids available in the extract. This strengthens the "Solvent Polarity-Phytochemical-Bioactivity Cascade" principle; in this case, the use of ethanol as a phytochemical solvent results in much higher extract bioactivity.

3.4. Exceptional Inhibition of Metabolic Enzymes: A Strong Case for Therapeutic Application

Of particular interest were the enzyme inhibition assays that elucidated the medicinal value of the ethanolic extract in the treatment of the studied metabolic disorders (Table 4).

In the α-glucosidase inhibition assay, the ethanolic extract performed the best, with an IC50 of 0.181 mg/mL. The aqueous extract was more than 20 times weaker, with an IC50 of 3.672 mg/mL. More importantly, the crude ethanolic extract was more than twice as potent as Acarbose, an IC50 of 0.411 mg/mL, which is a pharmaceutical drug used to treat type 2 diabetes. 1 In the lipase inhibition assay, the ethanolic extract, which had an IC50 of 2.968 mg/mL, also performed well. This was better than the aqueous extract (IC50 of 4.843 mg/mL) and was almost equivalent to the pharmaceutical control, Orlistat, which had an IC50 of 1.894 mg/mL.

Table 4: Comparative Inhibition of Metabolic Enzymes by *G. pentaphyllum* Extracts

Enzyme Inhibition Assay	IC50 (mg/mL)		
	Ethanolic Extract	**Aqueous Extract**	**Positive Control**
α-Glucosidase	0.181±0.003	3.672±0.034	0.411±0.053 (Acarbose)
Pancreatic Lipase	2.968±0.526	4.843±0.956	1.894±0.714 (Orlistat)

Values are presented as mean ± SD.

The unique therapeutic value of profound α-glucosidase inhibition is noteworthy. This enzyme is found in the brush border of the small intestine, where it cleaves carbohydrates into their constituent absorbable monosaccharides, including glucose. By inhibiting this enzyme, the glucose surge during the digestion of carbohydrates on the blood steam is reduced, which is fundamental for the management of type 2 diabetes during post-prandial hyperglycemia. It is impressive to note that the traditional use of *G. pentaphyllum* for diabetes is supported by the traditional use of *G. pentaphyllum*, which is the eloquent example of how a crude plant extract can exceed the performance of a purified pharmaceutical drug.

This remarkable outcome calls for further scientific investigations. The high potency may be an exclusive trait of the *G. pentaphyllum* chemotype cultivated under the unique soil and climatic conditions in Da Lat, Vietnam, indicating a possible "Geographic Varietal Significance," whereby a plant's "terroir" enhances its medicinal vigor. What is more, the presence of this action in a crude extract raises the "Synergy vs. Specific Compound Question." Is this remarkable inhibition due to a single highly active gypenoside or flavonoid, or is it due to the synergistic interplay of multiple compounds, whereby the total effect exceeds what any single constituent could produce? Responding to this question is the next logical step for drug discovery, which entails verifying claims from ethnomedicine to modern phytopharmaceuticals. The process of bioassay-guided fractionation would be appropriate, in which a crude extract is serially partitioned to its individual chemical components, and each fraction is re-evaluated for activity to determine the individual constituent(s) responsible for high α-glucosidase inhibition.

4. Conclusion

The results presented in this study indicate that the method of extraction transforms the phytochemical composition, and biological activities of *G. pentaphyllum*. For example, the ethanolic extract of that Vietnamese varietal is undoubtedly more advanced than the traditional aqueous extract in all the biological parameters assessed, which includes, antimicrobial, antioxidant, and α-glucosidase and lipase inhibition activities. This extract's biological activities are due to its abundance and diversity of phytochemicals that are elevated in flavonoids, phenolic compounds, and the entire spectrum of saponins found in the plant.

The most significant aspect of this research is the ethanolic extract's α-glucosidase inhibitory activity. Its potency of inhibition eclipses that of the clinically used drug Acarbose, thereby providing strong ethos to the ethnobotanical application of *G. pentaphyllum* in the treatment of diabetes. This extract, therefore, has strong potential for formulation as a novel and potent, phytopharmaceutical, or functional food ingredient for type 2 diabetes. Its lipase inhibitory activity makes it also useful in the context of metabolic syndrome, which includes obesity and hyperlipidemia.

In integration with the supplied evidence, the extraction and structural elucidation is warranted. Principal bioassay guided ethanol fractionation is advised. It is also crucial to simultaneously carry out a detailed phytochemical analysis of the said Vietnamese variety to quantify using HPLC-MS the primary gypenosides and flavonoids. Additionally, beyond the impressive *in vitro* findings achieved, the fundamental steps require the *in vivo* assessment of the diabetes and obesity animal models to validate the effectiveness, dose-response, and safety of the extract.

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