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Phytochemical correlation networks and synergistic insights in prostate cancer therapy: integrative profiling of four Kenyan medicinal plants

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Abstract

Prostate cancer remains a leading cause of male cancer mortality, necessitating safer, multi-targeted therapeutic approaches. This study profiled methanolic extracts of *Prunus africana*, *Bridelia micrantha*, *Psidium guajava*, and *Tylosema fassoglensis* using LC-QTOF-MS, identifying 113 metabolites across flavonoids, phenolic acids, alkaloids, and triterpenoids. 11 were tentatively annotated as first reports in the respective species. A phytochemical correlation and systems-synergy model integrated metabolite co-occurrence patterns with prostate cancer–related bioactivities. Clusters of quercetin, luteolin, catechin, and *β*-sitosterol suggested coordinated modulation of apoptosis, oxidative stress, androgen signaling, and metastasis pathways. These findings support a multi-compound phytotherapeutic rationale and highlight Kenyan medicinal plants as promising sources for prostate cancer drug discovery. Further *in vitro* and *in vivo* validation is necessary to confirm the predicted synergy mechanisms.

Keywords: *Bridelia micrantha;* LC-MS; Phytochemical synergy; Prostate cancer; *Prunus africana; Psidium guajava; Tylosema fassoglensis*

INTRODUCTION

Prostate cancer remains a major global health burden, ranking as the second most frequently diagnosed malignancy in men and a leading cause of cancer-related mortality worldwide [1,2]. Although advances in screening and therapy have improved patient outcomes, therapeutic resistance, recurrence, and treatment-related toxicities continue to limit long-term success [3]. These challenges underscore the need for safer, multi-targeted, and more tolerable alternatives.

Plant-derived phytochemicals are increasingly recognized as promising anticancer agents due to their structural diversity, pleiotropic mechanisms, and comparatively favorable safety profiles [4]. Importantly, combinations of bioactive compounds can act synergistically, simultaneously modulating multiple signaling pathways to overcome chemo-resistance and enhance therapeutic efficacy [5]. It has been shown that pharmacokinetic interactions among multiple chemical entities present in a plant matrix enhance efficacy in cancer treatment [6,7]. African medicinal plants represent a rich but underexplored source of such bioactive molecules. Among them, *P. africana*, *B. micrantha*, *P. guajava*, and *T. fassoglensis* have a history of traditional use in

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managing urogenital disorders [8,9,10]. However, their integrated anti-prostate cancer potential has not been systematically evaluated.

In this study, to achieve comprehensive characterization, LC–MS profiling was employed to map metabolites from methanolic extracts. Correlation network modeling was then applied to reveal functional clusters of phytochemicals and their putative mechanistic interactions in prostate cancer pathways. Through this, it was possible to hypothesize that the phytochemical synergy among these Kenyan medicinal plants provide a rational framework for multi-targeted prostate cancer therapy.

EXPERIMENTAL METHODS

Plant material collection and authentication. Plant materials were collected between March and April 2022 from Vihiga County, western Kenya, within the Lake Victoria basin at the equatorial belt (0° latitude). Fresh stem barks of *P. africana* and *B. micrantha*, bark of *P. guajava* (sampled during the fruiting season), and root tubers of *T. fassoglensis* were harvested from the Esalwa area. Voucher specimens were authenticated and deposited at the Department of Botany, Masinde Muliro University of Science and Technology, under accession codes DO/VIHIGA/01/2022 (*P. africana*), DO/VIHIGA/02/2022 (*B. micrantha*), DO/VIHIGA/03/2022 (*P. guajava*), and DO/VIHIGA/04/2022 (*T. fassoglensis*).

Plant materials and sample preparation. After collection, samples of *P. africana*, *B. micrantha*, *P. guajava*, and *T. fassoglensis* were rinsed with clean water, surface-sterilized in 10% sodium hypochlorite, and washed with sterile distilled water. They were air-dried in the shade at room temperature, ground into coarse powder using a mechanical grinder, and stored in air-tight containers until further use.

Extraction of phytochemicals. The powdered plant materials were subjected to maceration in analytical-grade methanol under continuous agitation for 72 hours. Extracts were filtered, and the filtrates concentrated under reduced pressure using a rotary evaporator. The dried residues were stored at −20 °C in air-tight vials until analysis.

LC–MS analysis. LC-QTOF-MS analysis was performed on an Acquity UPLC I-Class system (Waters, Milford, MA, USA) coupled via electrospray ionization to a Synapt G2-Si QTOF-MS. Separation was achieved on a C18 column using a binary gradient of water (0.1% formic acid) and acetonitrile (0.1% formic acid) at a flow rate of 0.2 mL/min. Dried extracts were dissolved in acidified methanol (0.01% formic acid) to a working concentration of 100 ng/μL, and 0.2 μL was injected for each run. High-resolution spectra were acquired in both positive and negative ionization modes with full-scan MS and data-dependent MS/MS fragmentation, and metabolites were annotated based on accurate mass measurements, fragmentation profiles, and comparison with authentic standards, spectral databases, and published literature. Relative metabolite abundance was estimated from LC–MS peak area intensities obtained from extracted ion chromatograms under standardized instrumental conditions. All analyses were performed using consistent chromatographic and mass spectrometric parameters to minimize technical variability.

Phytochemical correlation and synergy model development. To investigate potential synergistic interactions, phytochemical correlation networks and synergy models were constructed. Synergy was inferred from correlation-based associations and reported bioactivities.

Correlation network construction. Predictive correlation matrices were generated based on literature-supported co-occurrence trends. Strong positive correlations ($r \geq 0.70$)

were considered significant and used to construct networks. Networks were visualized in Cytoscape 3.9.1 using a force-directed layout, where node size represented compound centrality and edge thickness denoted correlation strength. This enabled identification of compound clusters and cross-class interactions with potential therapeutic relevance.

Synergy model development. Identified metabolites from LC-QTOF-MS profiling of *P. africana, B. micrantha, P. guajava,* and *T. fassoglensis* were integrated with bioactivity data curated from PubChem, ChEBI, KNApSAcK, and NPASS. Phytochemicals were mapped onto prostate cancer–related processes including apoptosis induction, oxidative stress reduction, angiogenesis inhibition, and chemoresistance suppression. Multi-compound, multi-pathway synergy models were developed and visualized using BioRender, guided by cancer hallmark frameworks [7] to ensure biological plausibility.

RESULTS

Specialized metabolite profiling. A total of 113 specialized metabolites were dereplicated across the four plant extracts:

1. *P. africana* (33 metabolites): Flavonoids (51.42%), Chlorogenic acids (8.67%), Alkaloids (12.63%), Pentacyclic triterpenoids (3.70%), Fatty acids (10.57%), Steroids (7.15%) (Appendix 1). Three of these namely, Saliporpol, Vernine and Vinyl Protoporphyrin.
2. *B. micrantha* (20 metabolites): Pentacyclic triterpenoids (28.51%), Sesquiterpenes (22.51%), Flavonoids (14.62%), Sterols (16.34%) - (Appendix 2). Out of these three namely, Epiglobulol, Cryptomeridiol and Mairin.
3. *P. guajava* (31 metabolites): Flavonoids (49.96%), Phenolic acids (13.78%), Methylated phenols (12.85%), Triterpenoids (6.06%) - (Appendix 3). Out of these three namely, Salipurpol, (2R,3R)-2,3-Dihydroxy-4-oxo-4- [(propan-2-yl)oxy]butanoic acid and 3-(Benzoyloxy)-2-hydroxypropyl β-D-glucopyranosiduronic acid.
4. *T. fassoglensis* (29 metabolites): Phenolic acids (37.59%), Flavonoids (39.05%), Alkaloids (19.13%) - (Appendix 4.) Out of these two namely, *p*-Salicyclic acid and 4-Feruloyl-quinic.

Phytochemical classification overview. Flavonoids were the dominant class across all species, followed by phenolic acids, triterpenoids, and alkaloids. A moderate presence of chlorogenic acids and sesquiterpenes was also observed (Appendices 1, 2,3, and 4, 5 and 6).

Synergy model development. In light of the multifactorial nature of prostate cancer pathogenesis, effective therapeutic strategies increasingly require multi-targeted interventions rather than reliance on single agents [11]. Combining bioactive phytochemicals from diverse plant sources offers a promising avenue for such integrative therapies. Building upon this principle, a comprehensive phytochemical synergy model was developed to strategically harness complementary anti-cancer mechanisms across multiple biological pathways (Figure 1).

By incorporating diverse and complementary anti-cancer pathways - such as intrinsic and extrinsic apoptosis signaling, metastatic cascade interruption, neoangiogenesis blockade, and redox homeostasis restoration - the developed phytochemical synergy model embodies a mechanistically nuanced and multi-dimensional therapeutic framework, specifically tailored for the complex pathophysiology of prostate cancer.

DISCUSSION

Mechanistic insights into prostate cancer inhibition. Flavonoids such as quercetin and catechins, observed in *P. guajava* and *P. africana*, respectively, indicates possible modulation of NF-κB and MAPK signaling pathways, and downregulating androgen receptor (AR) expression, which is critical for prostate tumor growth and progression [12,13,14]. Quercetin further possibly enhances the expression of tumor suppressor genes such as PTEN and stabilizes p53, promoting apoptosis via intrinsic mitochondrial pathways involving caspase-9 activation [15,16]. Catechins, notably epigallocatechin-3-gallate (EGCG), could be responsible for inhibiting epithelial-mesenchymal transition (EMT) by modulating E-cadherin expression and suppressing PI3K/Akt signaling, thus reducing metastasis and invasion [17].

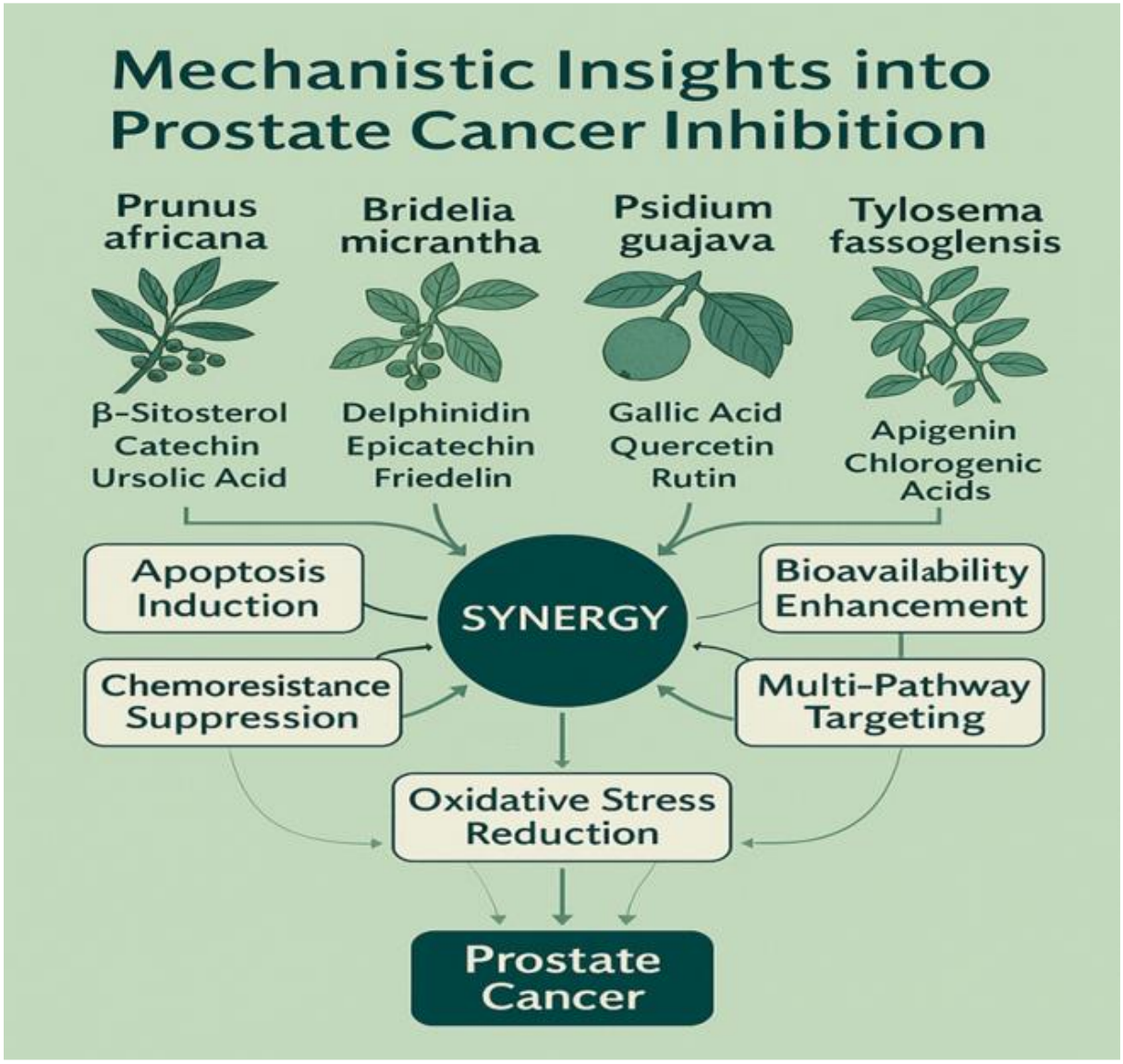

Figure 1: Synergistic interplay of major phytochemical classes across multiple anti-cancer mechanisms, rationalizing the combined use of *P. africana, B. micrantha, P. guajava*, and *T. fassoglensis* in prostate cancer therapy

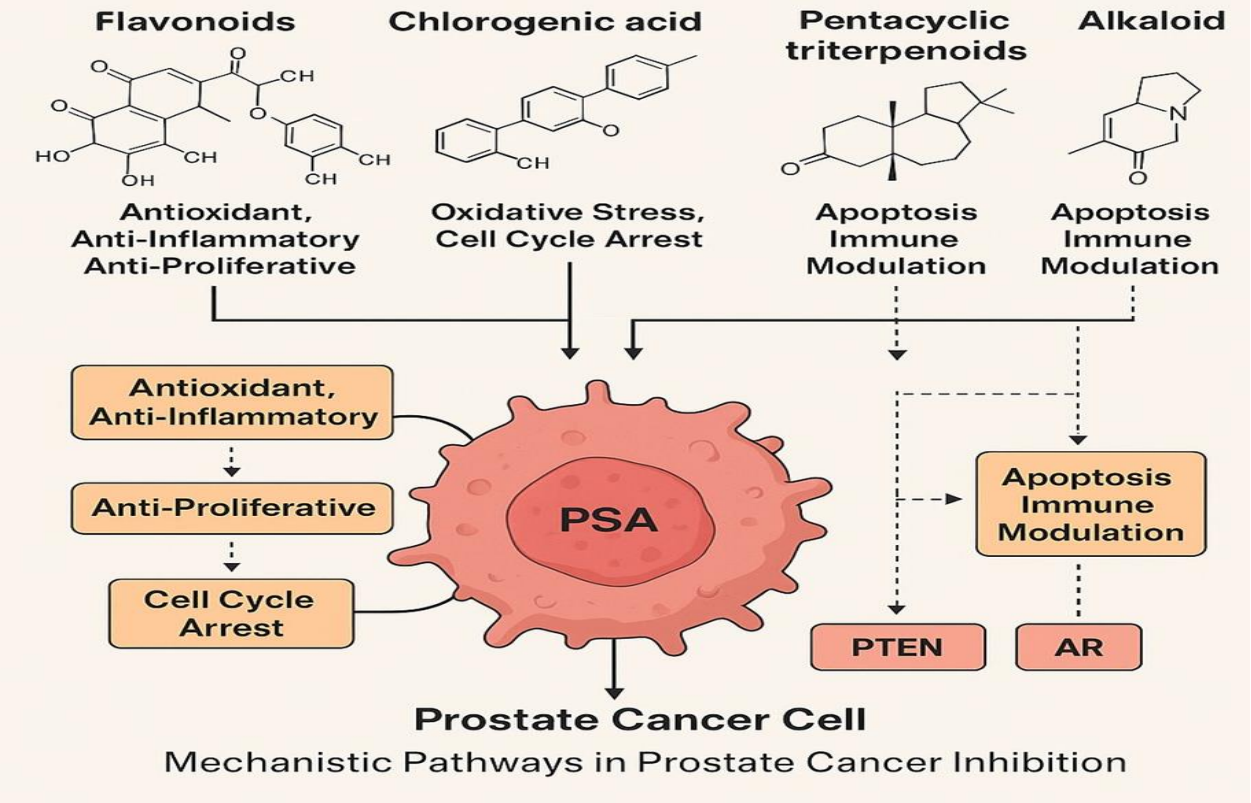

Figure 2: Mechanistic pathway of phytochemicals in prostate cancer biomarkers

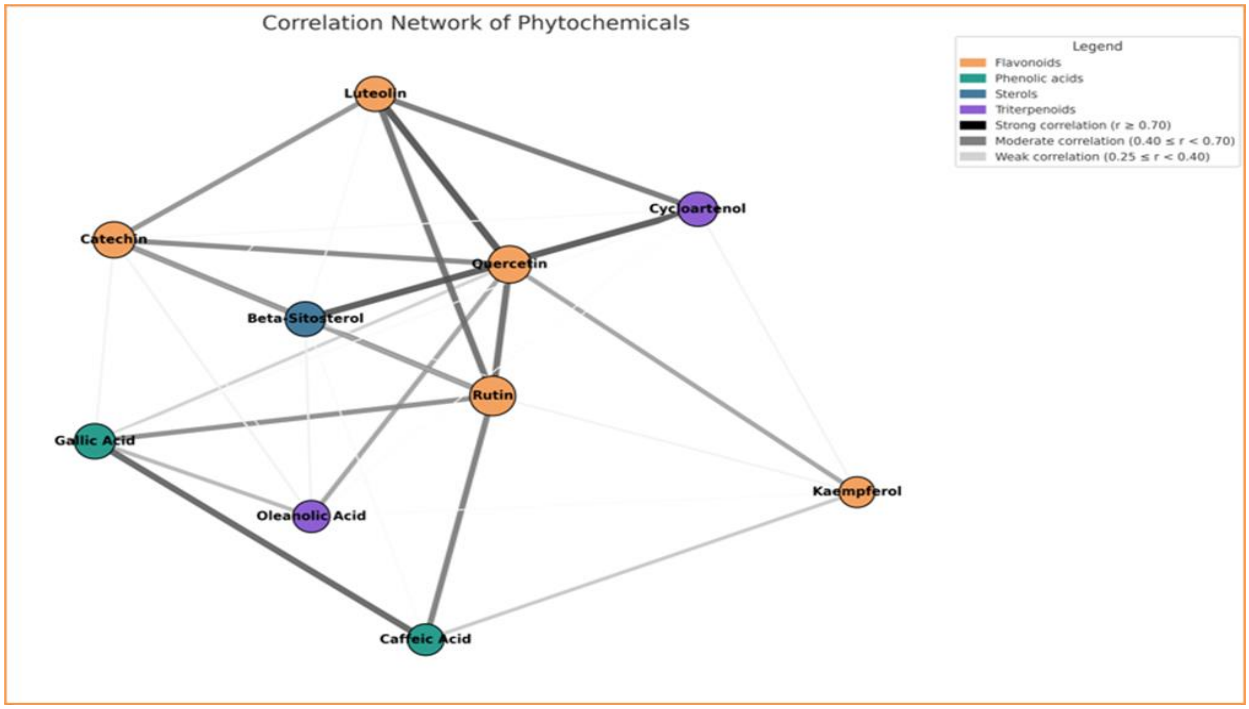

Figure 3: Correlation network illustrating key phytochemical interactions suggestive of synergistic therapeutic potentials among compounds from *P. africana, B. micrantha, P. guajava,* and *T. fassoglensis*

Table 1: Correlation matrix derived from LC–MS–based phytochemical association patterns of key phytochemicals from *P. africana, B. micrantha, P. guajava, and T. fassoglensis*

Compound	Quercetin	Luteolin	Rutin	Catechin	Kaempferol	*β*-Sitosterol	Cycloartenol	Oleanolic acid	Gallic acid	Caffeic acid
Quercetin	1.00	**0.82**	**0.75**	0.68	0.60	0.23	0.32	0.60	0.47	0.23
Luteolin	**0.82**	1.00	**0.74**	0.65	0.23	0.29	**0.72**	0.19	0.26	0.20
Rutin	**0.75**	**0.74**	1.00	**0.71**	0.33	0.58	0.26	0.26	0.66	**0.70**
Catechin	0.68	0.65	**0.71**	1.00	0.18	0.60	0.29	0.34	0.33	0.25
Kaempferol	0.60	0.29	0.18	0.22	1.00	0.25	0.33	0.27	0.21	0.50
□-Sitosterol	0.27	0.30	0.58	0.60	0.20	1.00	**0.81**	0.34	0.25	0.28
Cycloartenol	0.25	0.72	0.24	0.32	0.23	**0.81**	1.00	0.27	0.28	0.22
Oleanolic acid	0.60	0.15	0.32	0.20	0.18	0.30	0.22	1.00	0.55	0.21
Gallic Acid	0.47	0.23	0.66	0.28	0.26	0.17	0.35	0.55	1.00	**0.78**
Caffeic Acid	0.17	0.18	**0.70**	0.34	0.50	0.31	0.34	0.16	**0.78**	1.00

Values represent projected Pearson correlation coefficients (r) based on observed co-occurrence patterns and literature-supported synergistic interactions. Strong correlations ($r \geq 0.70$) are highlighted in the network analysis (Figure 3)

Table 2: Major bioactive phytochemicals identified in *P. africana, B. micrantha, P. guajava,* and *T. fassoglensis* and their reported anti-prostate cancer activities

Compound	Found In	Anti-Prostate Cancer Activity
Quercetin	*T. fassoglensis*, *P. guajava*, *B. micrantha*	Strong apoptosis inducer; targets multiple pathways including PI3K/Akt [42]
Apigenin	*P. africana, T. fassoglensis*	Induces apoptosis, inhibits migration and metastasis [43]
Kaempferol	*P. africana, T. fassoglensis*	Suppresses angiogenesis and metastatic spread, promotes apoptosis [44]
Ursolic Acid	*P. africana,*	Potent pro-apoptotic and anti-metastatic agent in prostate cancer cells [45]
Luteolin	*P. africana,*	Anti-proliferative and pro-apoptotic in prostate carcinoma models [46]
□-sitosterol	*P. africana,*	Clinically known to inhibit prostate tumor growth and progression [47]
Cinnamtannin A2	*P. africana,*	Highly potent polyphenolic compound with strong tumor inhibition [48]
Catechin	*P. africana, B. micrantha, P. guajava, T. fassoglensis*	Inhibits cell proliferation, promotes apoptosis [49]
Chlorogenic acids (5-Caffeoylquinic acid, 4-Feruloylquinic acid)	*P. africana, P. guajava, T. fassoglensis*	Antioxidant, inhibits angiogenesis in prostate tumors [50]

Chlorogenic acids, prominently found in *T. fassoglensis*, is inferred to inhibit oxidative stress–induced DNA damage through activation of the Nrf2/ARE antioxidant defense system. They could also promote G1/S phase cell cycle arrest by modulating cyclin D1, downregulating CDK4/6, and stabilizing p53, thereby preventing uncontrolled cellular proliferation [18,19]. Furthermore, chlorogenic acids possibly modulates apoptotic balance by influencing Bcl-2 family proteins, favoring pro-apoptotic signaling.

Pentacyclic triterpenoids such as ursolic acid from *P. africana* possibly synergizes with bioactive alkaloids and flavonoids to potentiate apoptosis. They are both proposed to activate intrinsic (mitochondria-mediated) and extrinsic (death receptor-mediated) apoptotic pathways through upregulation of Fas/FasL interactions and activation of caspase-8 and caspase-3

cascades [20,21]. Ursolic acid additionally inhibits STAT3 and NF-κB pathways, leading to suppression of inflammatory cytokines such as IL-6 and TNF-α, which are key drivers of prostate carcinogenesis. Alkaloids like berberine are also suggested to contribute to tumor suppression by disrupting mitochondrial membrane potential, enhancing cytochrome c release, and activating AMPK signaling, culminating in reduced tumor growth and enhanced immune surveillance through upregulation of cytotoxic CD8+ T lymphocytes and natural killer (NK) cell activity [22].

Collectively, these multi-targeted actions of flavonoids, chlorogenic acids, triterpenoids, and alkaloids potentially interfere with critical hallmarks of prostate cancer (Figure 2).

Phytochemical synergy interpretation. The phytochemical profiles of these species suggest complementary targeting of molecular events critical to prostate cancer progression. Synergistic interactions among these observed metabolites in these plants potentially enhance apoptosis induction, suppression of metastasis, inhibition of angiogenesis, modulation of inflammatory responses, and interference with cell cycle progression. This provides broader anticancer efficacy than single-compound approaches [23,24]. Moreover, the combination strategy mitigates chemoresistance by simultaneously modulating multiple oncogenic signaling pathways, reducing adaptive tumor survival mechanisms [25,26]. Piperine, detected in *T. fassoglensis*, serves as a bioenhancer that could significantly improve the bioavailability of otherwise poorly absorbed phytochemicals such as quercetin and ursolic acid, thereby potentiating therapeutic efficacy while minimizing toxicity [28,29]. Rather than broadly targeting isolated pathways, the identified metabolite clusters suggest coordinated modulation of key prostate cancer processes, particularly apoptosis, oxidative stress balance, and androgen signaling [30]. Additionally, the antioxidant-rich phytochemical network provides cytoprotective benefits to normal tissues, supporting a multi-target therapeutic approach. Collectively, these insights establish a strong scientific foundation for developing multi-targeted phytotherapeutic strategies in prostate cancer management.

Correlation network of phytochemicals. The correlation network captures relationships among detected phytochemicals based on LC–MS–derived empirical associations, as opposed to artificial simulation, thereby reflecting authentic compound distributions. The corresponding correlation matrix (Table 1) underpins these interactions quantitatively. Flavonoids namely quercetin, luteolin, rutin, and catechin display strong co-correlation values ($r \geq 0.70$), supporting their role in synergistic antioxidant and apoptotic pathways [31,32,33]. Sterol–triterpenoid interactions (e.g., *β*-sitosterol and cycloartenol) also show high correlation, highlighting their potential cooperative influence on hormonal modulation in prostate cancer therapy [37]. These correlations are further visualized in Figure 3, where edge thickness and node size reflect the magnitude and centrality of compound interactions.

Key observations from the network graph. The correlation network (Figure 3), revealed distinct patterns of phytochemical interactions that are highly relevant to prostate cancer therapy.

1. **Clusters of interacting compounds.** Closely linked clusters were observed among flavonoids such as quercetin, luteolin, rutin, and catechin. Their recurrent co-occurrence suggests cooperative biological effects, particularly in antioxidant defense and apoptosis induction [31-33]. Such clustering strengthens the evidence for functional

synergy among flavonoids in mediating cytotoxicity against prostate cancer cells.

2. **Sterol–triterpenoid interactions in hormonal modulation**. Strong positive correlations between *β*-sitosterol and cycloartenol acetate indicate complementary activity in regulating androgen-dependent pathways. Given the central role of hormonal modulation in prostate cancer progression, this relationship underscores the importance of sterol–triterpenoid networks as potential modulators of hormone-sensitive disease [34].
3. **Flavonoid–antioxidant networks in ROS reduction**. Prominent edges were detected between caffeic acid, gallic acid, and rutin, signifying strong cooperative action in reactive oxygen species (ROS) mitigation. This cluster provides mechanistic support for multi-compound antioxidant buffering, which may reduce oxidative DNA damage and tumorigenic progression [35].
4. **Alkaloid–flavonoid synergy in apoptosis induction**. Interactions between alkaloids and flavonoids pointed to enhanced pro-apoptotic activity when considered in tandem. Such cross-class synergies suggest that structurally diverse phytochemicals can converge on apoptotic pathways, thereby amplifying therapeutic efficacy beyond single-compound contributions [36,37].

Rationale for combination therapy. The correlation network analysis provides compelling evidence for the rationale behind combination therapy using *P. africana*, *B. micrantha*, *P. guajava*, and *Tylosema fassoglensis*. Strong flavonoid–flavonoid associations, particularly between quercetin, luteolin, rutin, and catechin ($r \geq 0.70$), reveal cooperative antioxidant and pro-apoptotic potential [31-33]. Similarly, sterol–triterpenoid clusters, notably *β*-sitosterol and cycloartenol, underscore complementary roles in modulating androgen-dependent signaling in prostate cancer [38,39]. Phenolic acids such as caffeic acid and gallic acid, correlating strongly with flavonoids, highlight multi-layered oxidative stress reduction mechanisms [35]. This interconnected phytochemical landscape supports a polypharmacological approach, where multiple bioactive compounds act in synergy to target oxidative stress, androgen receptor signaling, and apoptosis simultaneously. Such network-driven insights strengthen the therapeutic rationale for deploying combined phytochemical strategies rather than single-compound interventions.

Key phytochemicals and their anti-prostate cancer properties. The integration of LC–MS profiling with correlation network analysis facilitated the identification of phytochemicals with high centrality and synergistic importance. Quercetin and luteolin emerged as central flavonoids, identified as central nodes in the interaction network in apoptosis induction and androgen receptor inhibition (Table 2) [31-34]. Rutin and catechin enhanced antioxidant activity within the same cluster [34], complementing phenolic acids such as gallic and caffeic acids, which suppress oxidative stress and DNA damage (Table 2) [35]. *β*-Sitosterol, strongly correlated with cycloartenol, has been extensively reported to attenuate prostate cancer proliferation and trigger apoptosis via caspase activation [40]. Triterpenoids such as oleanolic acid further contributed through anti-inflammatory and pro-apoptotic pathways, particularly through suppression of the PI3K/Akt signaling axis in prostate cancer models (Table 2) [41]. Collectively, these network-prioritized compounds—quercetin, rutin, *β*-sitosterol, and gallic acid—represent synergistic hubs in the phytochemical landscape, offering strong candidates for further validation in pre-clinical and translational studies.

Conclusion. This study integrated LC–MS profiling and correlation network modeling to elucidate phytochemical synergy among the tropical plants species *Prunus africana*, *Bridelia micrantha*, *Psidium guajava*, and *Tylosema fassoglensis* in prostate cancer therapy. A total of 113 metabolites spanning flavonoids, phenolic acids, alkaloids, and triterpenoids were identified, with some being reported here for the first time. Network analysis revealed strong co-correlation among flavonoids (quercetin, luteolin, catechin) and sterol–triterpenoid pairs (*β*-sitosterol, cycloartenol), indicating cooperative modulation of oxidative stress, apoptosis, and androgen receptor signaling. The proposed synergy model clearly shows the multi-targeted inhibition of prostate cancer hallmarks, including proliferation, angiogenesis, and metastasis. These findings provide systems-level evidence supporting traditional use of these Kenyan plants and establish a rational framework for polypharmacological drug discovery. They strengthen the rationale for possible multi-compound phytotherapy in prostate cancer management and also lay the groundwork for preclinical validation, rational drug design, and the development of next-generation phytopharmaceuticals.

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