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In Silico Study of Palm Fruit (*Elaeis Guineensis*) Identification of Secondary Metabolites (Knapsack): Activity and Toxicity (Way2drug)

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Abstract

Palm kernel fruit (*Elaeis guineensis*) is a small, low-yield fraction of the fruit that is often considered waste, but is thought to contain pharmacologically valuable secondary metabolites. This study aims to map the secondary metabolites of palm kernel meal using KNApSAcK and predict their activity and toxicity using PASS Online and GUSAR Online.The study was conducted by searching for metabolites in KNApSAcK Metabolomics, predicting biological activity in PASS (threshold Pa ≥ 0.7), and evaluating acute toxicity in five exposure routes using GUSAR, then analyzed descriptively, quantitatively, and qualitatively. A total of 15 metabolites were identified, including phenolic acids (4-hydroxybenzoic acid), saturated/unsaturated fatty acids (lauric, myristoleic, palmitoleic), carotenoids (alpha-carotene), vitamin E (delta-, beta-, gamma-, alpha-tocopherol) and tocotrienols (alpha-, beta-, delta-, gamma-tocotrienol), diterpenoids (Gibberellin A110), and volatile terpenes (isoprene). PASS predictions highlight antioxidant activity and lipid peroxidation inhibition; alpha-tocotrienol shows high scores as a reductant (0.979) and lipid peroxidase inhibitor (0.977). GUSAR toxicity estimates indicate that the majority of compounds are classified as OECD class 4–5 for the oral route with relatively high LD50 values, including alpha-tocopherol (4790 mg/kg) and palmitoleic acid (4906 mg/kg).

Keywords; Palm kernel; *Elaeis guineensis*; in silico.

1. Introduction

The need for natural-based therapeutic candidates continues to increase, while much of the low-value tropical biomass remains underutilized as a source of bioactive compounds. In the oil palm [1] ecosystem, the historical focus on high-value streams has led to the relative neglect of low-yield fractions such as sand fruit, despite indications that its secondary metabolite content holds promise for pharmacological exploration [2] . Thus, the issue raised is the knowledge gap regarding the bioactive potential of sand fruit and the opportunities for valorizing residual fractions to promote a circular bioeconomy [3][4].

Contextually, Indonesia, as a major palm oil producer, has a strategic interest in downstreaming low-value biomass into functional health products. Literature evidence shows that palm fruit matrix contains carotenoids, tocopherols/tocotrienols, phenolic acids, and fatty acids related to antioxidants and membrane protection, but the specific profile of palm fruit as a separate matrix is still minimal [2], [5],[6],[7]. Therefore, the targeted research gap is the mapping of metabolites and preliminary estimation of the safety activity of palm kernel shells through rapid screening before wet verification [8], [9].

To address this gap, this study applied an in silico approach as an initial structure-based filter to predict the spectrum of activity and acute toxicity. KNApSAcK Metabolomics was used for metabolite annotation and SMILES extraction, PASS Online for cross-endpoint activity probability (Pa) estimation, and GUSAR for multi-route acute LD50 prediction with applicability domain control [8][10], [11]. This framework establishes explicit decision thresholds, such as Pa ≥ 0.7 and oral LD50 ≥ 1000 mg/kg, making the candidate prioritization process transparent and auditable.

Conceptually, the contribution of this research is twofold. First, the study repositions sand fruit from a mere productivity liability to a bioactive reservoir with a species-metabolite database-based metabolite map and modern toxicology predictions [2],[11]. Second, the research operationalizes replicable selection logic based on applicability domain screening and an integrated priority index that can be transferred to other underutilized plant fractions [8], [9]. Methodologically, the in silico descriptive design includes: metabolite extraction from KNApSAcK, activity screening by PASS with Pa criteria, toxicity estimation via GUSAR in multiple routes, and combined scoring to nominate candidates for further testing [5],[6].

With this framework, this study provides a theoretical contribution in the form of clarification of the phytochemical landscape and predicted activity-safety envelope in sand fruit as a different biological matrix, as well as a practical contribution in the form of a priority list of candidates and a screening framework that can guide targeted in vitro/in vivo testing and the design of nutra/cosmeceutical formulations [3], [4].

2. Methodology

This study applies a descriptive in silico computational design that is structured in parallel with the sequence of results: starting from searching and curating a list of sand fruit metabolites, followed by predicting biological activity spectra, then estimating acute toxicity across exposure routes, and ending with the integration and prioritization of candidates for further testing [9][12]. In the initial stage, metabolite data were extracted from a species–metabolite database and curated specifically for the fruit matrix, with standardization of structural identity (SMILES/InChI) to ensure interoperability between applications [13]. All validated structures were then processed to predict the probability of activity (Pa) at various pharmacological endpoints using standard parameters and explicit selection thresholds (e.g., Pa ≥ 0.7) to ensure consistent and auditable screening [5],[14]. The next step estimates acute LD50 for several animal-model exposure routes and marks the applicability domain (AD) status to maintain caution in interpreting predictions [12]. Activity and toxicity results are combined in a structured worksheet, then a combined priority score is calculated that normalizes the number of priority activities along with the safety profile (e.g., oral LD50 ≥ 1000 mg/kg) and penalties for predictions outside the AD [6]. The analysis was performed descriptively in quantitative terms (Pa distribution, proportion of priority activity per chemical class, LD50 range and class per route) and qualitatively (pharmacological relevance and safety implications), and all steps were documented (application version, access date, file formats, raw outputs) to ensure replication [15]. Technical subsection:

A. Equipment and materials

1. Hardware: computer/laptop with adequate specifications (modern CPU, RAM ≥ 4–8 GB), stable internet connection.
2. Software: plant metabolite database platform (latest version), biological activity prediction application, acute toxicity prediction application, and spreadsheet for integrating results [9].
3. Materials: curated list of sand fruit metabolites (identifier, SMILES/InChI) specific to the fruit matrix [13].

B. Parameters and thresholds

1. Activity: use default prediction parameters and set a selection threshold of Pa ≥ 0.7 to identify priority activities [5],[14].
2. Toxicity: set the initial safety criterion LD50 oral ≥ 1000 mg/kg as a safety margin indicator; record class and AD status [12].
3. Applicability domain: mark predictions outside the AD as limited; do not use them as the basis for primary decisions (Szewczyk et al., 2021)[6].

C. Candidate selection criteria

1. At least two activities with Pa ≥ 0.7 at relevant endpoints (e.g., antioxidant/anti-inflammatory) [5].
2. Meets the criterion of oral LD50 ≥ 1000 mg/kg and is within the AD for the intended route [12].
3. High combined priority score based on activity weight, safety, and AD status [6].

D. Brief replication steps

1. Metabolite extraction: search species, download species–metabolite relations, curate fruit-specific entries, and export SMILES/InChI [13].
2. Activity prediction: upload SMILES batch, save Pa/Pi outputs per endpoint, flag activities with Pa ≥ 0.7 [9],[14].
3. Toxicity prediction: run LD50 estimates across routes; export values, classes, and AD status [12].
4. Integration: combine results into a master spreadsheet; calculate priority scores; document parameters, application versions, access dates, and input–output files in the appendix [15].

3. Result and Discussion

3.1. Result

Table 1. Metabolite Profile: Main Activities (PASS) and Estimated Oral Toxicity (LD_{50} GUSAR)

Metabolite	Main Activities (PASS)	LD50 Oral (GUSAR) + classification
4-Hydroxybenzoic acid	Lipid peroxidase inhibitor; Antioxidant	2291 mg/kg – Class 5
Lauric acid	CYP2J substrate; Mucomembranous protector	2799 mg/kg – Class 5
Myristoleic acid	Membrane integrity agonist; Antiseborrheic	4505 mg/kg – Class 5
Palmitoleic acid	Lipid peroxidase inhibitor; Antioxidant	4906 mg/kg – Class 5
Alpha-Carotene	Reductant; Antioxidant	5783 mg/kg – Non Toxic (Class tinggi)
Delta-Tocopherol	Lipid peroxidase inhibitor; Peroxidase inhibitor	2600 mg/kg – Class 5
Beta-Tocopherol	Reductant; Antioxidant	3803 mg/kg – Class 5
Gamma-Tocopherol	Lipid peroxidase inhibitor; Antioxidant	3618 mg/kg – Class 5

Alpha-Tocopherol	CYP2J substrate; Retinol acyltransferase inhibitor	4790 mg/kg – Class 5
Gibberellin A110	Reductant; Enzyme inhibitor (BCO1/FTK)	556 mg/kg – Class 4
Alpha-Tocotrienol	Reductant; Lipid peroxidase inhibitor	4790 mg/kg – Class 5
Beta-Tocotrienol	Peroxidase inhibitor; CYP2C12 substrate	2769 mg/kg – Class 5
Delta-Tocotrienol	Reductant; Lipid peroxidase inhibitor	2537 mg/kg – Class 5
Gamma-Tocotrienol	Peroxidase inhibitor; Lipid peroxidase inhibitor	2777 mg/kg – Class 5
Isoprene	Antineoplastic; Antieczematic	863 mg/kg – Class 4

3.2. Discussion

The findings show a coherent pattern of bioactivity between groups of compounds that is physiologically significant: Carotenoids and vitamin E (tocopherols/tocotrienols) consistently rank highest in PASS activity as lipid peroxidation inhibitors/antioxidants, in line with their role as membrane protectors and radical chain breakers in lipophilic environments [5],[6],[14]. While fatty acids (lauric, myristoleic, palmitoleic) exhibit membrane integrity protection, hypolipemic potential, and enzymatic involvement (CYP2J/CYP2C12), explaining their pharmacokinetic relevance and potential nutrient–drug interactions [16]. This convergence reinforces the hypothesis that the palm kernel fruit matrix provides synergistic antioxidants (carotenoids, tocopherols, tocotrienols) and membrane stabilizers (fatty acids), thereby potentially reducing oxidative stress and improving lipid homeostasis at the cellular level [5],[14].

On the risk side, GUSAR predictions indicate a wide oral safety margin for almost all compounds (OECD classes 4–5, LD50 thousands of mg/kg), making the consumption route the most viable; exceptions such as Gibberellin A110 and isoprene (class 4) indicate the need for dose control and additional verification [17]. Compared to 2020 literature reporting the antioxidant/hypolipemic effects of tocotrienols and the benefits of carot enoids, this pattern is consistent and enriches the evidence with a specific list of metabolites and their toxicological estimates [5],[6],[14]. It also opens space for further research to test compound synergies, evaluate bioavailability, and map CYP interactions implied by PASS annotations, including safety considerations for vitamin E dosing in adults [7].

4. Conclusion

This study mapped the secondary-metabolite profile of buah pasir kelapa sawit and, through in silico prediction, clarified its functional potential: a coherent antioxidant and anti-lipid-peroxidation core driven by carotenoids and vitamin E isomers, complemented by membrane-stabilizing and lipid-modulating actions of key fatty acids. Taken together, these findings indicate a plausible protective role against oxidative and metabolic stress under physiologically relevant exposure, while acute oral safety margins are broadly supportive of nutraceutical development pathways.

The contribution of this work lies in integrating compound-level identification with activity and toxicity prediction to prioritize candidates for translation, thus progressing from descriptive phytochemistry to decision-ready shortlists and hypotheses on mechanism

(antioxidant defense, membrane integrity, and selected metabolic enzyme interactions). Future research should validate top candidates in vitro/in vivo (efficacy, dose–response, and synergy), characterize ADME and CYP interactions, and test formulation strategies to improve bioavailability ultimately linking biomarker changes to clinically meaningful outcomes.

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