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**Original Research Article**

# *In silico* Assessment of Drug-like Properties of Alkaloids from *Areca catechu* L Nut

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## *Abstract*

***Purpose:*** *To investigate in silico the drug-like properties of alkaloids (arecoline, arecaidine, guvacine, guvacoline, isoguvacine, arecolidine and homoarecoline) obtained from the fruits of Areca catechu L (areca nut).*
***Methods:*** *All chemical structures were re-drawn using Chemdraw Ultra 11.0. Furthermore, software including Bio-Loom for Windows - version 1.5, Molinspiration Property Calculator and ACD/I-LAB service were used to predict the drug-like properties of the alkaloids, including relative molecular mass (MW), partition coefficient log P (cLog P), number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), topological polar surface area (TPSA), number of rotatable bonds (NROTB), pKa, and aqueous solubility at a given pH (LogS). In addition, Lipinski's rule was used to evaluate drug-like properties.*
***Results:*** *From our research, MWs of the seven compounds were all < 500. HBD and cLog P values of the seven compounds were all < 5, and HBA values were all < 10. In addition, TPSA value of each compound was < 60 Å$^2$, and NROTB value was < 10. Besides, pKa values of the seven alkaloids were > 7.5; furthermore, they possess good solubility at pH 1.0, 5.0, and 7.0.*
***Conclusion:*** *All the seven alkaloids possess good drug-like properties, and demonstrated good oral absorption and bioavailability. The results also suggest that these compounds can be further developed into new oral drugs for treating certain diseases.*

***Keywords:*** *Areca catechu L, Areca nut, Drug-like properties, Alkaloids, Arecoline, Arecaidine, Guvacine, Guvacoline, Isoguvacine, Arecolidine, Homoarecoline, In silico*

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## INTRODUCTION

The fruit of *Areca catechu* L (areca nut), belonging to Arecaceae family, is an important folk medicine used in China to treat parasitic diseases, digestive disorders, and edema [1,2]. In addition, areca nut currently is one of the most important traditional Chinese medicines (TCM) in the Pharmacopoeia of the People's Republic of China [3]. Modern pharmacological investigations have demonstrated that areca nut possesses several bioactivities including anti-parasitic effect [4], digestive effect [5,6], anti-depressive effect [7], anti-oxidant effect [8], anti-bacterial effect [9], anti-inflammatory and analgesic effects [10].

Previous phytochemical studies reported that areca nut contains various chemical compounds that mainly include alkaloids [11] and tannins [12]. Moreover, alkaloids have been demonstrated as the main active constituents

responsible for the pharmacological actions of areca nut [2,13].

Besides good pharmacological effects, ideal drugs should possess a good bioavailability profile including solubility, permeability, lipophilicity, pKa, and stability [14]. Drug-like properties researchers have mainly investigated the bioavailability profiles of candidate compounds [15]. To the best of our knowledge, there has been no investigation on the drug-like properties of alkaloids of areca nut, and this has limited the development of its constituents. Therefore, the objective of the present stud was to investigate the drug-like properties of alkaloids of areca nut (see Figure 1), namely, arecoline, arecaidine, guvacine, guvacoline, isoguvacine, arecolidine, and homoarecoline using an *in silico* method.

## EXPERIMENTAL

### Data sources for *in silico* assessment

The seven pyridine-type alkaloids of Areca nut, viz, arecoline, arecaidine, guvacine, guvacoline, isoguvacine, arecolidine, homoarecoline, were assessed in the present investigation. All chemical structures of the seven compounds were re-drawn using Chemdraw Ultra 11.0 (Cambridge Soft Corporation, MA, USA) and converted to MOL files before application to each assess software.

### *In silico* assessment software used and determination rules

The Bio-Loom for windows version 1.5 (BioByte Corporation, CA, USA), Molinspiration Property Calculator [16], and ACD/I-LAB service (Advanced Chemistry Development, UK) were used to predict the drug-like parameters for the seven alkaloids. These parameters include relative molecular mass (MW), partition coefficient log P (cLog P), number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), topological polar surface area (TPSA), number of rotatable bonds (NROTB), pKa, and aqueous solubility at a given pH (LogS).

Lipinski's rules were used to evaluate the drug-like properties [17] while good absorption or permeation of candidate drugs were predicted globally according to the following criteria [17]: (1) Not more than 5 H-bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms); (2) Not more than 10 H-bond acceptors (nitrogen or oxygen atoms); (3) A molecular weight (MW) under 500 (g/moL); (4) A partition coefficient log P (cLog P) < 5.

In addition, a drug can be absorbed over 90 % if the TPSA value is < 60 $Å^2$ [18]. The NROTB value of a candidate drug is also very important for its absorptive ability, and a good absorption might be predicted by a NROTB value < 10 [19]. The solubility was also evaluated by determining LogS value.

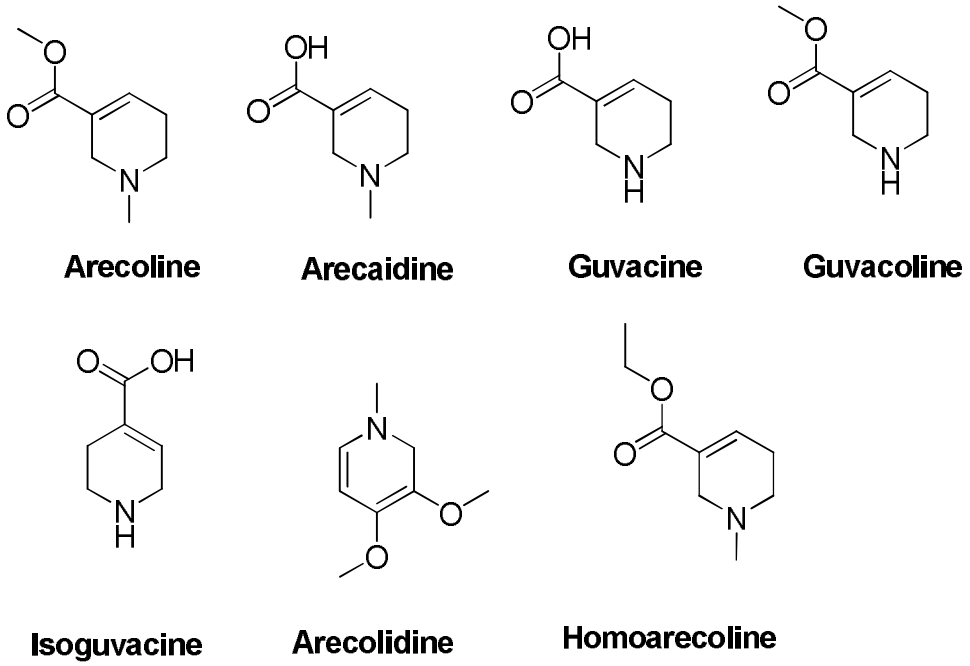


**Figure 1:** Chemical structure of the alkaloids of areca nut

## RESULTS

According to our present investigation, the *in silico* predictive results of drug-like properties of alkaloids from areca nut are shown in Table 1 and Table 2. The MV of each of the seven compounds including arecoline, arecaidine, guvacine, guvacoline, isoguvacine, arecolidine and homoarecoline, was < 500. The number of hydrogen bond donors and cLog P values of the seven compounds was also < 5 while the number of hydrogen bond acceptors was < 10, TPSA values of the seven compounds were all less than 60 $Å^2$, and NROTB were all < 10. These predicted results indicate that the seven alkaloids possess potential good oral absorption and that their absorptivity would be > 90 %.

The pKa values of the arecoline, arecaidine, guvacine, guvacoline, isoguvacine, arecolidine, and homoarecoline were 7.84 ± 0.40, 8.44 ± 0.20, 9.43 ± 0.20, 8.94 ± 0.40, 10.05 ± 0.20, and 7.92 ± 0.40, respectively; thus, they are all > 7.5. Furthermore, the solubility of each of the seven alkaloids was also predicted *in silico*. However, the results revealed that only three alkaloids - arecoline, guvacoline and homoarecoline - exhibited good solubility at all the test pH of 1.0, 5.0, and 7.0.

## DISCUSSION

In our present investigation, we firstly studied the drug-like properties of the seven alkaloids from areca nut *in silico*, and found that the three alkaloids including arecoline, guvacoline and homoarecoline, were predicted to possess good drug-like properties, indicating that these alkaloids may possess good oral absorption and bioavailability.

Nowadays, it is well known that an ideal candidate drug should possess some good characteristics of absorptive property and bioavailability besides pharmacological activity [20]. In addition, it is estimated that less than 2 in 10000 candidate drugs are authorized for treatment of diseases, and computer-aided drug design (CADD) can be used to improve the current situation of drug development by using in silico assessment [16,17]. In recent drug screen strategy, the *in silico, in vivo*, and *in vitro* are commonly used together in the early high throughput screening (HTS) (Figure 2). The *in silico* results can be used to predict the *in vivo* and *in vitro* experiments, and can also predict the drug-like properties of the candidate drugs.

**Table 1:** Constitutive properties of the alkaloids of areca nut

| Compound | MW (≤500) [a] | cLogP (≤5) [a] | HBD (≤5) [a] | HBA (≤10) [a] | TPSA [b] (≤140 $Å^2$) [a] | NROTB (≤10) [a] | pKa |
|---|---|---|---|---|---|---|---|
| Arecoline | 155.19 | 0.90 | 0 | 3 | 29.50 | 2 | 7.84 ± 0.40 |
| Arecaidine | 141.17 | -1.75 | 1 | 3 | 40.50 | 1 | 8.44 ± 0.20 |
| Guvacine | 127.14 | -2.30 | 2 | 3 | 49.30 | 1 | 9.43 ± 0.20 |
| Guvacoline | 141.16 | 0.49 | 1 | 3 | 38.30 | 2 | 8.94 ± 0.40 |
| Isoguvacine | 127.14 | -2.84 | 2 | 3 | 49.30 | 1 | 10.05 ± 0.20 |
| Arecolidine | 155.19 | 1.11 | 0 | 3 | 21.70 | 2 | 4.24 ± 0.60 |
| Homoarecoline | 169.22 | 1.43 | 0 | 3 | 29.50 | 3 | 7.92 ± 0.40 |

*[a] criteria filter for good oral absorption; [b] a drug with TPSA <60 $Å^2$ will be completely absorbed, Fa > 90%.* ***Note:*** *MW = relative molecular mass; logD = the apparent logP values at a given pH; HBD = number of hydrogen bond donors; HBA = number of hydrogen bond acceptors; TPSA = topological polar surface area; NROTB = number of rotatable bonds; pKa = the values of the acid-base dissociation constant*

**Table 2:** Solubility of alkaloids of areca nut

| Compound | LogS (pH1.0)[c] and solubility (g/L) | LogS (pH5.0)[c] and solubility (g/L) | LogS (pH 7.0)[c] and Solubility (g/L) |
|---|---|---|---|
| Arecoline | 0.81 (1000) | 0.81 (1000) | -0.42 (58.7) |
| Arecaidine | 0.85 (1000) | -1.05 (12.6) | -1.04 (12.9) |
| Guvacine | 0.90 (1000) | 0.008 (12.5) | -1.02 (12.1) |
| Guvacoline | 0.85 (1000) | 0.85 (1000) | 0.75 (800) |
| Isoguvacine | 0.90 (1000) | -0.98 (13.4) | -0.99 (12.9) |
| Arecolidine | 0.60 (615.2) | -1.31 (7.62) | -1.38 (6.52) |
| Homoarecoline | 0.77 (1000) | 0.77 (1000) | -0.79 (27.7) |

*[c] LogS value in the biological pH range: pH 1.0 (stomach), pH 5.0 (duodenum) and pH 7.0 (jejunum); salivary pH varies between 5.5 and 7.0, depending on the flow rate.* ***Note:*** *LogS = aqueous solubility at a given pH (Log mol/L); solubility (g/L)*

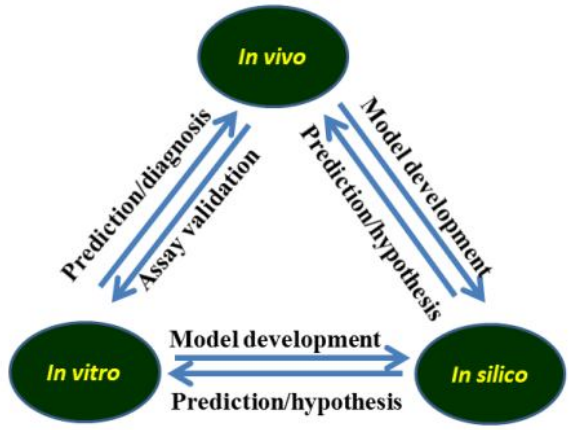


**Figure 2:** Relationship of the *in vivo*, *in vitro*, and *in silico* experiments

Drug-like properties mainly include solubility, permeability, lipophilicity, pKa and stability. The solubility, permeability, lipophilicity, and TPSA are the main factors for bioavailability of oral drugs [21,22]. Currently, Lipinski's rule is widely used in evaluating the drug-like properties of candidate drugs in database and guiding to screen orally bioavailable drugs [19]. Lipinski's rules states that oral bio-availability of a drug is likely to exist if it possesses the following features: MW ≤ 500; H-bond donors ≤ 5; H-bond acceptors ≤ 10; c logP values ≤ 5. In the present study, our results *in silico* predicted that all the seven alkaloids of areca nut obeyed the Lipinski's rules. In addition, our results demonstrated that the pKa values of the seven alkaloids were higher than 7.5, indicating that these compounds can exist in intestinal tract (pKa value were 7.3) in a non-ionic form. Solubility can directly affect the *in vivo* bioavailability of oral administered drugs, and a low solubility is the main reason for losing activity *in vivo*. According to the results of the present investigation, three alkaloids - arecoline, guvacoline and homoarecoline – possess good solubility at pH 1.0, 5.0, and 7.0, which indicates that these compounds can easily dissolve in stomach (approx. pH 1.0), duodenum (approx. pH 5.0), and jejunum (approx. pH 7.0).

Therefore, based on based on all the parameters evaluated, three alkaloids of areca nut, namely, arecoline, guvacoline and homoarecoline possess good drug-like properties.

## CONCLUSION

Arecoline, guvacoline and homoarecoline possess good drug-like properties, and show good oral absorption and bioavailability. Therefore, these compounds can potentially be further developed into new oral drugs for treating some diseases.

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