Xeronine structure and function: computational comparative mastery of its mystery

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Abstract Morinda citrifolia (Noni) fruit has a long history of dietary use in tropical regions of the world. Pharmacological properties that have been attributed to the fruit include anti-inflammatory, anti-cancer, and antioxidant properties. Xeronine, a small alkaloid which has been patented (US4543212) is one of the bioactive compounds of Noni fruit, which is believed to be capable of modifying the molecular structure of specific inactive proteins thereby regulating proper folding to active enzymes. Despite reports of the potential of Xeronine as therapeutic agent, its presence is controversial and its structure has not been explored. In this study, standard chemoinformatics tools and servers such as ChemSketch, ChemMine, SwissTargetPrediction, SwissADME and SwissSimilarity have been employed to predict its possible structure. In addition, synthetic xeronine structures based on the known bioactive components of Noni fruit were designed. Results showed that the hypothetical structure of xeronine provided by the patent inventor is a mystery based on its \(<5\%\) probable protein targets and no similarity match to the US Food and Drug Administration (FDA) approved drugs and experimental compounds by in silico evaluation. By contrast, final designed xeronine structure possess all the features that were described in the patent document, and has \(\geq40\%\) probable protein targets related to neurodegenerative diseases such as Alzheimer’s disease (AD), which possibly justifies the key function stated in the patent.

Keywords Morinda citrifolia · Noni fruit · Xeronine · De novo drug design · Cheminformatics

Introduction

Morinda citrifolia Linn. (Rubiaceae family), popularly called Noni or Indian mulberry, is a small tropical tree that grows widely in Polynesia, and is typically found in Hawaiian and Tahitian islands. It has been used in folk remedies for over 2000 years. All parts of the plant (leaves, fruit, bark and root) have several pharmacological properties (Saraphanchotiwitthaya and Sripalakit 2015). The fruit has a long history of dietary use in tropical regions throughout the world (Wang et al. 2002).

Noni juice was accepted in the European Union as a novel food in 2002 (Dussossoy et al. 2011). Since then, Noni juice market has continued to grow, the fruits contain active components such as phenolic compounds, particularly coumarin, flavonoid, and iridoid compounds (Saraphanchotiwitthaya and Sripalakit 2015). Pharmacological properties that have been attributed to the fruit include anti-inflammatory, anti-cancer, and antioxidant properties. Its fruits have been used as a folk medicine for the treatment of many diseases including diabetes, high blood pressure, inflammation, and cancer.

Ralph Heinicke demonstrated that the Noni fruit contains a natural precursor for xeronine which is called proxeronine (Heinicke 1985). Proxeronine is converted to the alkaloid, xeronine, in the body by an enzyme named proxeroninase, which required activation by specific amidoase and proper concentration of free calcium ions to
modify its stricture to dimeric or trimeric form (Heinicke 1985). Heinicke described this alkaloid as a critical normal metabolic coregulator, and suggested that xeronine could be cure for nicotine and hard drug addiction. He described critical beneficial application of xeronine in the alleviation of the symptoms of typical senility (Heinicke 1985). In the presence of insulin, xeronine activates the peripheral cell membrane insulin receptors and assist the normal absorption of glucose (Sridevi et al. 2013).

The misfolding and aggregation of proteins are thought to be a major cause of synaptic loss and neuronal death observed in different neurodegenerative diseases (Maiti et al. 2014). Gradual accumulation of denatured or misfolded proteins over time leads to progressive loss of structure and/or function of neurons and ultimately neuronal death. The aggregation of misfolded proteins is highly regulated by both genetic and environmental factors (Maiti et al. 2014). Recently, there has been a focus on small molecules/drugs, bioactive phytochemicals, which can impact proteostasis and also exert neuroprotection through antioxidant and anti-inflammatory activities (Maiti et al. 2014).

Xeronine, a small alkaloid which has been patented (US4543212), is one of the active compounds of Noni fruit which is believed to be able to modify the molecular structure of specific inactive proteins by regulating proper folding to active enzymes (Heinicke 1985).

Despite report of the potential of xeronine as a therapeutic agent, its existence is controversial because its structure has not been studied. Structural and biochemical studies on xeronine so far has not been available in literature. The hypothetical structure of xeronine (Fig. 1) obtainable was proposed in an unpublished communication (Heinicke 2001).

In the post-genomic era, benefiting from the dramatic increase in bio-macromolecule and small molecule information, computational tools has been applied to most aspects of the drug discovery and development process, from target identification and validation to lead discovery and optimization (Sanni and Fatoki 2017). In this study, we computationally evaluate the structure and functions of xeronine as a potential therapeutic agent.

Materials and methods

Preparation of ligands

The hypothetical structure of xeronine was obtained online from (https://www.psiram.com/de/index.php/Xeronin) and reconstructed using the chemically intelligent drawing interface freeware developed by Advanced Chemistry Development, Inc., (http://www.acdlabs.com). Using draw mode of Chemsketch, ligand structures were generated and the three dimensional optimizations were done. SMILES (Simplified Molecular Input Line Entry Specification) was generated for the reconstructed xeronine structure and saved for further analysis.

Structural comparative analysis

The constructed structure of xeronine was compared with known bioactive components of Noni fruit which include rutin, quercetin, kaempferol, scopoletin, and rubiadin 1-methyl ether obtained by LC–MS/MS (Pandi et al. 2015). The SMILES of the structure of these bioactive compounds were obtained from NCBI PubChem Compound (http://www.ncbi.nlm.nih.gov/pccompound), and were analyzed using ChemMine tools (http://chemmine.ucr.edu/similarity) developed by Backman et al. (2011).

Computational design and clustering analysis

The synthetic xeronine was designed computationally using Chemsketch, by combinatorial integration of the components obtained from structural comparative analysis of constructed xeronine and other bioactive compounds of Noni. Clustering analysis was performed using ChemMine tools (http://chemmine.ucr.edu/) developed by Backman et al. (2011).

ADMET/Tox screenings

ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) screening helps in detecting drug likeliness of compounds (Sanni and Fatoki 2017). The SMILES format of the ligands was loaded into the SwissADME server (http://www.swissadme.ch) and ADME screening was performed at default parameters (Daina et al. 2017).

![Fig. 1 Hypothetical structure of xeronine](image-url)
**Potential protein target analysis**

The potential protein target analysis for xeronine was carried out at the SwissTargetPrediction server (http://www.swisstargetprediction.ch) using the SMILES format of each constructed structure, and Homo sapiens was selected as the source of target (Gfeller et al. 2013).

**Similarity search**

The designed xeronine with potential protein target was compared to the available approved and experimental drugs database respectively using Swisssimilarity server (http://www.swisssimilarity.ch) (Zoete et al. 2016).

**Result and discussion**

A critical step in the design of hybrid designed multi-target ligand (DML) is the careful choice of pharmacophores for the individual targets and the linker to interconnect them (Morphy and Rankovic 2006). In this study, two different structures were constructed (C1 and C2) from hypothetical structure of xeronine to assure precision (Fig. 2a, b), and it was observed that some of its components were similar to other bioactive components of Noni fruit, when compared using the maximum common substructure (MCS) algorithm of the similarity server, which often provides the most accurate and sensitive similarity measure, especially for compounds with large size differences (Backman et al. 2011). The tanimoto coefficient has a range from 0 to 1 with higher values indicating greater similarity than lower ones, and rutin showed highest similarity followed by kaempferol, and quercetin as shown in Table 1.

Clustering of compounds by structural or property similarity can be a powerful approach to correlating compound features with biological activity. Clustering tools are also widely utilized for diversity analyses to identify structural redundancies and other biases in compound libraries. Multi-dimensional scaling (MDS) clustering methods provided by ChemMine Tools are based on the R programs cmdscale while the MDS output encodes this information in a scatter plot (Backman et al. 2011). The evaluation of designed structures (D1–D6) showed those ones that fall into the cluster of other bioactive components of Noni fruit (Fig. 3).

The summary of computational ADME/Tox screenings result of the constructed and designed xeronine together with other bioactive components of Noni fruit (Table 2) indicated that C1 and C2 were less lipophilic (XlogP) with low gastrointestinal absorption (GA) and lower potential of being synthesized from organic sources due to high synthetic accessibility score (S) compared to other known bioactive components of Noni fruit. The synthetic accessibility score (S) ranges between 1 (easy to make) and 10 (very difficult to make). The partition coefficient (LogP) and solubility coefficient (LogS) interplay to define the bioavailability score (BS).

Simply, for a drug-like compound, 5 ≤ lipophilicity ≥ 0 ≤ hydrophilicity ≥−5, according to Lipinski’s rule (Lipinski et al. 2001) one violation (LV) is acceptable for all the designed xeronine structures. Only D1, D2, D3 and D6 satisfied the condition for safe synthetic xeronine compound, this was also observed from the result of potential protein target (Table 3). C1, C2, D4 and D5 have less than five percent potential protein targets and no similarity match to the Food and Drug Administration (FDA) approved drugs and experimental compounds by in silico evaluation (Table 4).

The results show that the hypothetical structure of xeronine that was provided by the patent inventor is a mystery based on its less than five percent probable protein targets from in silico evaluation. The D3 and D6 structures fitted the functions of xeronine that have been documented (Heinicke 1985) based on probable protein targets which include microtubule-associated protein tau, tyrosyl-DNA phosphodiesterase 1, muscleblind-like protein 1, muscarinic acetylcholine receptor M1, and cyclin-dependent kinase 1. Since these target proteins are liable to misfolding, these designed structures of xeronine could function as it has been documented.

**Fig. 2 a** Xeronine structure C1. **b** Xeronine structure C2
Based on the structure of xeronine chemistry described in the patent as well as the results of comparative and clustering analysis in this study, we designed a synthetic xeronine structure which contains modified adenine linked to isomaltose molecule by $N$-glycosyl bond, that has SMILES notation of OC4C(COC1OC(CO)C(O)C(O)C1O)OC(n3ccc2cncnc23)C(O)C4O (Fig. 4). This final designed xeronine structure has not been reported elsewhere in the scientific literatures. It possesses all the alkaloid features that were described in the patent document (Heinicke 2020).
Table 2 ADME/Tox of Xeronine and Noni Bioactive Compounds

| Structure | SMILES                                                                 | MW     | HA | AH | FC | RB | HBA | HBD | MR  |
|-----------|------------------------------------------------------------------------|--------|----|----|----|----|-----|-----|-----|
| Xeronine C1 | C12C34NC(NO1)NC(C4C1C(C(O2(O1)O)C3O)C0O)O                            | 303.27 | 21 | 0  | 1  | 1  | 10  | 7   | 72.55|
| Xeronine C2 | OCCI1CC2OC3(OCC1C1C(O)NC4NC1(C2O)C3O4)O                                | 317.3  | 22 | 0  | 1  | 1  | 10  | 7   | 77.36|
| Xeronine D1 | CC1OC=C(C=CC2CC=CC2C1)O                                             | 268.35 | 19 | 0  | 0.87 | 2  | 4  | 1   | 71.82|
| Xeronine D2 | OCCI1CC2OC3=CC2C1OC=C(C2O)COCC1O                                    | 272.29 | 19 | 0  | 0.85 | 1  | 6  | 3   | 64.94|
| Xeronine D3 | OCCI1CC2OC3(C2O)C1O1CC2CC2C1O                                      | 258.31 | 18 | 0  | 1   | 1  | 5  | 2   | 63.88|
| Xeronine D4 | OCCI1CC2OC(C2C1C1C2OC2)ONC2N1C1C(N2)O                                  | 345.39 | 24 | 0  | 1   | 2  | 9  | 5   | 92.75|
| Xeronine D5 | OCCI1CC2C1C=O1C1C2OC2ONC2N1C1C(N2)O                                   | 341.36 | 24 | 0  | 0.8 | 2  | 9  | 4   | 91.31|
| Xeronine D6 | OCCI1CC2OC3(C2C1CC12OCC2CC1C(O)O)O                                   | 314.37 | 22 | 0  | 1   | 1  | 6  | 3   | 77.36|
| Rutin (Ru) | CC1=CC(=C(C=C1C2=C(C(C=O1)OCC2C(C=C(C=C2O)O)O)O)O)O                  | 610.52 | 43 | 16 | 0.44 | 6  | 16 | 10  | 141.38|
| Quercetin (Qu) | C1=CC(=C(C=C1C2=C(C(C=O1)OCC2C(C=C(C=C2O)O)O)O)O)O                | 302.24 | 22 | 16 | 0   | 1  | 7  | 5   | 78.03|
| Kaempferol (Ka) | C1=CC(=C(C=C1C2=C(C(C=O1)OCC2C(C=C(C=C2O)O)O)O)O)O          | 286.24 | 21 | 16 | 0   | 1  | 6  | 4   | 76.01|
| Scopoletin (Sc) | C1=CC=C2C=CC(C=O1)C=CC=CC(=C1)=O                                    | 192.17 | 14 | 10 | 0.1 | 1  | 4  | 1   | 51  |
| Rubiadin 1-methyl ether (Rm) | C1C=C2C=C1O(C)=OC3=CC=CC=C3C2=O)O                                    | 268.26 | 20 | 12 | 0.12 | 1  | 4  | 1   | 73.23|

C constructed, D designed. Physicochemical properties: MW molecular weight, HA heavy atom, AH aromatic heavy atoms, FC fraction Csp3, RB rotatable bonds, HBA H-bond acceptors, HBD H-bond donors, MR molar refractivity, TPSA total polar surface area. Lipophilicity: XLOGP3. Water solubility: ESOL Log S. Pharmacokinetics: GA GI absorption. Druglikeness: LV lipinski violations, BS bioavailability score. Medicinal chemistry: LV leadlikeness violation, S synthetic accessibility
1985), and gave over forty percent probable protein targets that related to neurodegenerative diseases such as Alzheimer’s disease (AD), which potentially justifies the key function stated in the patent. It has low gastrointestinal absorption, average synthetic accessibility and high solubility, with potential protein targets that include adenosine receptors (A1, A2a, A2b, and A3), tyrosyl-DNA phosphodiesterase 1 (TDP1), adenosine deaminase, adenosine kinase, and muscleblind-like proteins 1.

Table 3 Potential protein targets of designed xeronine structures

| Target                                                      | Target uniprot ID | Xeronine D1 | Xeronine D2 | Xeronine D3 | Xeronine D6 |
|-------------------------------------------------------------|------------------|------------|------------|------------|------------|
| Microtubule-associated protein tau                          | P10636           | a          | a          | a          | a          |
| Cytochrome P450 19A1                                         | P11511           | a          |            |            |            |
| Sigma non-opioid intracellular receptor 1                   | Q99720           | a          |            |            |            |
| Tyrosyl-DNA phosphodiesterase 1                             | Q9NUW8           |            | a          |            | a          |
| Muscleblind-like protein 1                                  | Q9NR56           | a          | a          | a          |            |
| Adenosine receptor A3                                        | P33765           | a          |            |            |            |
| Tyrosine-protein phosphatase non-receptor type 1 and 2      | P17706, P18031   | a          |            |            |            |
| Histone deacetylase 1                                       | Q13547           | a          |            |            |            |
| Muscarinic acetylcholine receptor M1                         | P11229           | a          |             |            | a          |
| Glycine receptor subunit alpha-1                            | P23415           | a          |            |            |            |
| Cyclin-dependent kinase 1                                   | P06493           | a          |            | a          |            |
| Glucosylceramidase                                           | P04062           | a          |            |            |            |

* 20–50% Probability on Target. Probabilities have been computed based on a cross-validation. They may therefore not represent the actual probability of success for any new molecule.

Table 4 Designed xeronine similarity data

| Xeronine | Similar small molecule | Drugbank ID | Score | Probable xeronine structure* |
|----------|------------------------|-------------|-------|------------------------------|
| D3       | Lactulose              | DB00581     | 0.301 | No                           |
|          | Didanosine             | DB00900     | 0.184 | Yes                          |
|          | Chloramphenicol        | DB00446     | 0.167 | No                           |
|          | Zidovudine             | DB00495     | 0.149 | Yes                          |
| D6       | Lactulose              | DB00581     | 0.270 | No                           |
|          | Pentostatin            | DB00552     | 0.032 | Yes                          |
|          | Penciclovir            | DB00299     | 0.026 | Yes                          |

* The nitrogen-containing ring of these small molecules could probably present in typical xeronine.

For example, adenosine receptor (AR) has been implicated in neurodegenerative diseases (Gomes et al. 2011), and cardiovascular diseases (Geldenhuys et al. 2017). Tyrosyl-DNA phosphodiesterase 1 (TDP1) has been implicated in cancer and spinocerebellar ataxia with axonal neuropathy (SCAN1), a neurodegenerative disorder that is inherited in an autosomal recessive pattern (Dexheimer et al. 2008; Huang et al. 2011). Moreover, synthesis and cellular characterization of this proposed structure by combination of methods (Meirer et al. 2017; Agudo et al. 1998) may provide further insight to the functionality of this novel designed xeronine. Our subsequent works will focus on in silico optimization and in vitro organic synthesis of this promising molecule.

**Conclusion**

Xeronine structure has not been deciphered till now, and the results from this study has shown that it may possibly exist naturally, and suggest that its organic synthesis is
practically possible for the management of neurological disorder. The designed xeronine in this study could be used as a reference for xeronine identification in various plant, animal and microbial sources during analysis on liquid chromatography mass spectrometry (LC–MS). This study has provided a basic understanding of the xeronine structure. It is hoped that further study involving organic synthesis, structural analysis, and wet-lab experiments, would provide better comprehension and improvement of the synthetic production and application of this compound as therapeutic agent.

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

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