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NeeMDB: Convenient Database for Neem Secondary Metabolites

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Abstract:
Indian Neem tree is known for its pesticidal and medicinal properties for centuries. Structure elucidation of large number of secondary metabolites responsible for its diverse properties has been achieved. However, this data is spread over various books, scientific reports and publications and difficult to access. We have compiled and stored structural details of neem metabolites in NeeMDB, a database which can be easily accessed, queried and downloaded. NeeMDB would be central in dissipating structural information of neem secondary metabolites world over.

Background:
Neem tree (*Azadirachta indica* A. Juss), native to Indian sub-continent, has long been recognized for its pesticidal and medicinal properties**[1, 2].** It has gained the distinction of being the most researched tree in the World. Extracts of neem fruit, seeds, seed kernels, twigs, stem bark and root bark have been shown to possess repellent, anti-feedant, insect growth regulatory (IGR), anti ovipositional, fecundity and fitness reducing properties on insects **[3]**. Many species of insects are known to be sensitized by neem formulations **[3, 4].** Diverse biological properties of neem are due to many secondary metabolites found in various parts of the tree. Major constituents of its metabolite pool such as Azadirachtin, Azadirone, Gedunin, Meliacarpin, Nimbin, Salannin, Vilasinin groups were proved to be significant pesticidal and/or medicinal principle **[5].** Crude extracts of neem are found to be more potent than pure Azadirachtin **[6]** suggesting there are many more compounds in the neem extract, which even at low concentration have potentiating abilities.

Searching information of each and every metabolite of neem is a formidable task as most of the details are scattered over many forms of literature. The most studied Azadirachtin, has a complex molecular structure which belongs to tetranortriterpenoid class and exist in many forms of which Azadirachtin A and Azadirachtin B **(Figure 1)** are well documented **[7].** Both secondary and tertiary hydroxyl groups and tetrahydrofuran ether are present and their molecular structures reveal 16 stereogenic centres, 7 of which are tetrasubstituted making the structure more complex. Similarly, most of neem secondary metabolites are triterpenoids and have complex structure. The epimers such as, Nimbidin and Nimbidinin, Salannolactame I and II, hydroxyazadiradione alpha and beta, Gedunin and DiepoxyAzadiradione, Isomargosinolide & Dihydrogedunin, are compounds with same molecular weight but structurally different which are all difficult to isolate and identify using conventional methods. To minimize manual work in searching biologically potent neem secondary metabolites, we have curated and developed Nee MDB (http://www.vmsrfdatabase.org/index.php), providing information on secondary metabolites from different parts of neem tree and other details such as their molecular structure, molecular formula, and physicochemical properties with appropriate references.

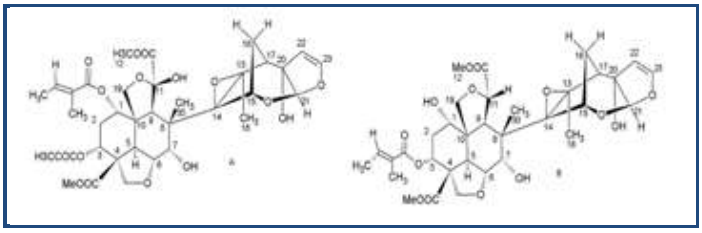

Figure 1: Two most prominent forms of Azadirachtin in neem

Methodology:
The NeeMDB contains information of 250 secondary metabolites collected from available scientific reports and published articles. The database is built on MolDB5R, a collection of fully functional PHP scripts for running a structure database with search options for text, functional groups, and structure/substructure/similarity. The "checkmol/matchmol" utility program **[8]** was used to create a web-based searchable structure database. Besides standard search capabilities (text, structure/substructure/similarity), "checkmol/matchmol" offers a fast additional search option, entirely based on binary pattern matching, which uses automatically assigned functional group descriptors, details of which is explained elsewhere **[8]**. Minimum software include, Browsers Firefox 10.0 or above or Chrome 27.0 or above; Java 6 or above.

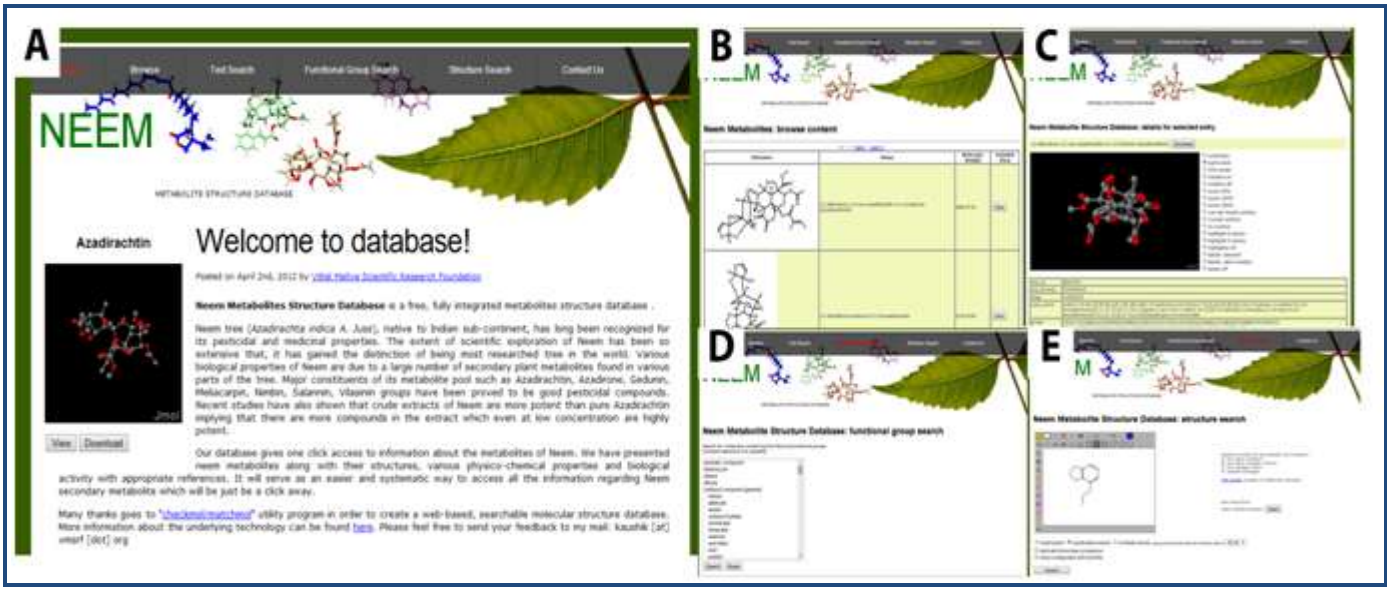

Figure 2: Front end of NeeMDB: **A)** Home page; **B)** Browse option; **C)** Details page; **D)** Functional group based searching; **E)** Structure based searching of the database.

Utility:
The NeeMDB will serve as an open access repository of published neem secondary metabolite information. One can easily browse for the target neem principle using the provided features (**Figure 2**), 1) list of 250 neem metabolites, 2) Sort the list according to either alphabetic or molecular weight (by clicking on the column heading), 3) Structure (2D and 3D) of the metabolites, 4) predicted clogP and IUPAC name, 5) Chemical functional group characterization and 6) Text & Structure based searching options.

Caveats:
The care was taken in proper assignment of stereo bonds and in performing 2D to 3D structure conversions. However, we urge users to refer to original publications for any fine details of the structure. Jmol, an open source JAVA applet is used to view molecules in 3D. Some browsers recognize Jmol as a threat and might block the application with following error "Your security settings have blocked an untrusted application from running". The 3D feature can be allowed by setting Java settings to Medium.

Future development:
Even after decades of research on neem, new secondary metabolites are being explained and added continuously. Efforts will be made to update the NeeMDB with newly defined neem metabolites on a regular basis. A simulated Mass Spectroscopy (MS) profile for all the compounds would help identify match such profiles in LC/MS profiles of crude neem extracts. Such a feature would be added in the next update.

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