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Natural Deep Eutectic Solvent (NADES) Design Framework for Extraction of Polyphenols from Jackfruit

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Jackfruit considered to be an underutilized fruit where around 60 % of it was dumped and this creates a critical waste disposal which highly affects the environment. NADES have been widely used in many applications and it has emerged as a new sort of green solvents used to replace the organic solvents with numerous advantages like simple preparation, sustainability and environmentally friendly. The main aim of this research is to develop a framework of NADES design for extraction of polyphenols from jackfruit by using computational approach combined with mathematical models. The research methodology is divided into 3 stages. Stage 1 is mainly about problem definition which required determining the needs for NADES and setting its target property values. Stage 2 is mainly focus on the development of databases which involving the prediction of target property values for both the NADES and polyphenols by either calculating using suitable property model which corresponding to the target properties or using computational approach such as COSMOtherm and TmoleX to obtain the missing information. In Stage 3, first screening process is based on the target properties of NADES and followed by second screening process which is based on their solvation performance in extraction of polyphenols and top 4 NADES were selected. This proposed method has been applied in a case study to select the top 4 NADES for the extraction of quercetin, artocarpin and gallic acid from jackfruit. From the case study, the relative solubility value of NADES 33 in quercetin, artocarpin and gallic acid from jackfruit is the highest which are 0.28547, 78.3101 and 0.0095 g/g. It showed that NADES 33 was the best extraction solvent for the polyphenols extraction in current database out from 51 NADES candidates.

1. Introduction

Artocarpus heterophyllus which also known as jackfruit, is one of the species belongs to the mulberry family (Moraceae). It consists of edible part which are pulp and seed and non-edible part which are rind and rachis (Wade, 2019). In Malaysia, the planted area as well as the yield for jackfruit has increased from year 2013 to 2018. In year 2018, Malaysia has produced 31,023 t of jackfruit (Ministry of Agriculture and Agro-based Industry, 2018). Jackfruit has many advantages such as it can be used for medicinal purposes, provide nutrients for human being and it can be process into diverse products like jams, beverages and preserves food The non-edible part takes up as much as 60 % of the whole fruit which are consider as the unutilized waste. In Kerala state in India, there are approximated 35 M of jackfruit waste are dumped annually. This dumping action has created a critical waste disposal and environmental problems (Sundarraj and Vasudevan, 2018). Besides, the flesh of jackfruit is highly perishable and often undergoes tissue softening and flavour loss which promotes more jackfruit waste to be disposed. This research can help to minimize the jackfruit waste by carry out the extraction of polyphenols from jackfruit.

NADES can be defined as a mixture which consist of two or three components that are typically plant-based primary metabolites to form a new chemical compound without reaction and it will hinder the crystallization process of each other with specific molar ratio (Gala et al., 2013). The interaction between the compounds occur through intermolecular hydrogen bonds which one acting as the hydrogen bond acceptor (HBA) and the other as the hydrogen bond donor (HBD) (Jeliński and Cysewski, 2018). Although ionic liquids (IL) and deep eutectic solvents were discovered as options to replace the organic solvents to be versatile solvents that used for diverse purposes but both the solvents still have some limitations to be applied in real chemical industry due to poor

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biodegradability, biocompatibility and sustainability. NADES have emerged as a new type of truly green solvents with many excellent advantages such as sustainability, biocompatibility, environment friendly, remarkable solubilizing power and outstanding designability. NADES are potentially to act as solvent in many fields such as extraction, biomass pre-treatment, pharmaceutical products, electrochemistry and biocatalyst (Dai et. al., 2013). This work focused on the screening and selecting of the top 4 NADES as extraction solvent for polyphenols from jackfruit for solvent design purpose. Nowadays, the application of NADES for extraction of phenolic compounds from plant increase rapidly. Extraction of flavonoids from Scutellaria baicalensis by using NADES has been conducted in recent study (Oomen et al., 2020). In another recent work, extraction of alkaloids and polyphenols from Pneumus boldus leaves using different NADES (Torres-Vega et al., 2020). Currently, the existing practice by most of the solvent extraction is trial-and-error experimental method which need to consume lots of time and cost. It is not practical to conduct the experiments in determining the most optimal NADES as repeated procedures are required as there are plenty of possible choices of NADES could be synthesized from different components (Rahman et al., 2020). In this study, NADES design utilized a computational approach to reduce the usage of laboratory test, prevent waste of materials and shorten operation time which can provide an easier and faster way for researchers to apply the best NADES in extraction of polyphenols.

2. Methodology

Methodology for NADES design framework for extraction of polyphenols from jackfruit has been developed as shown in Figure 1. This methodology consists of three major stages.

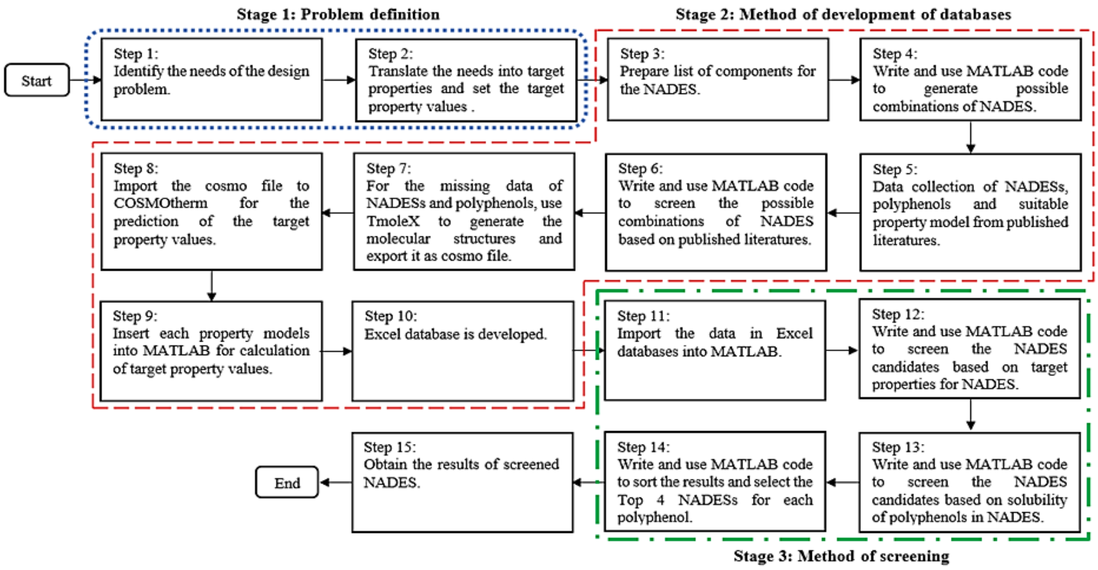

Figure 1: Step by step flowchart for methodology

2.1 Stage 1: Problem definition

In this stage, the needs of the NADES design have to identify by referring to the published literatures. Generally, the needs of the extraction solvent to be designed can be classified into three groups which are performance, safety and environmentally friendly. This is followed by translating the needs into its compatible target properties. For the target property constraints, it can be set in term of lower and upper boundary or as fixed values. The range of the target property values can be obtained from the literature search and by comparison with the existing solvents utilized for extraction process.

2.2 Stage 2: Method of development of databases

Two group of components were required to prepare for the combinations of NADES. MATLAB is used to determine the possible combinations that can generated from the list of components that have been prepared (MATLAB, 2018). An extensive search was done and data collection was performed for the NADES, polyphenols from jackfruit and suitable property models from published studies and reliable online database such as ChemSpider and PubChem. All the data obtained were stored in Excel database. After that, the possible combinations of NADES that generated from MATLAB were screened with those found in published literatures to eliminate the NADES without enough information. For the case that there are missing data for target properties of NADES and polyphenols from jackfruit, TmoleX software was utilized to generate the molecular structures of compounds. COSMOtherm software is then used for the prediction of the selected target property values. Next, the property models that selected were insert into MATLAB for calculation of target property values. The data that obtained were transferred into Excel database. The Excel databases were act as an input for this NADES design framework for extraction of polyphenols from jackfruit.

2.3 Stage 3: Method of screening

NADES candidates were reduce significantly based on the selected target properties in this stage. The first step was imported the database that have been developed in stage 2 into MATLAB. There are two screening part will be conducted in this stage. NADES candidates were first screened based on the constraints of target properties for NADES and followed by second screened based on the solubility of polyphenols in NADES. Elimination of NADES candidates were performed once their values are not within the range of constraints that have been set. The following step was arranged and sorted the NADES candidates according to their values of relative solubility from the greatest to lowest. Top 4 NADES were selected.

3. Results and discussion

3.1 Framework for user who wish to design NADES

Figure 2 presents the general NADES design framework for extraction of polyphenols from jackfruit for user. As not every user has the computational approach such as COSMOtherm and TmoleX software, they are encouraged to find the suitable property models to estimate the values of their desired target properties.
For the case which user would like to add extra components of NADES that are not including in this database, user may insert that selected component into the Excel database manually. By adding the extra components, more possible combination of NADES may occur. Users have to find the missing data of the new NADES formed themselves either using computational approach or mathematical model. This is important for user to ensure that they have enough information for the new NADES that just add into the database so that the data can transfer and proceed for screening process. If the user does not have any computational approach like TmoleX and COSMOtherm software, they can find the data of NADES from published study or using the property model suggested. For the user who have the TmoleX and COSMOtherm software, it will be much more easy and efficient way to find out the prediction target property values of NADES generated.

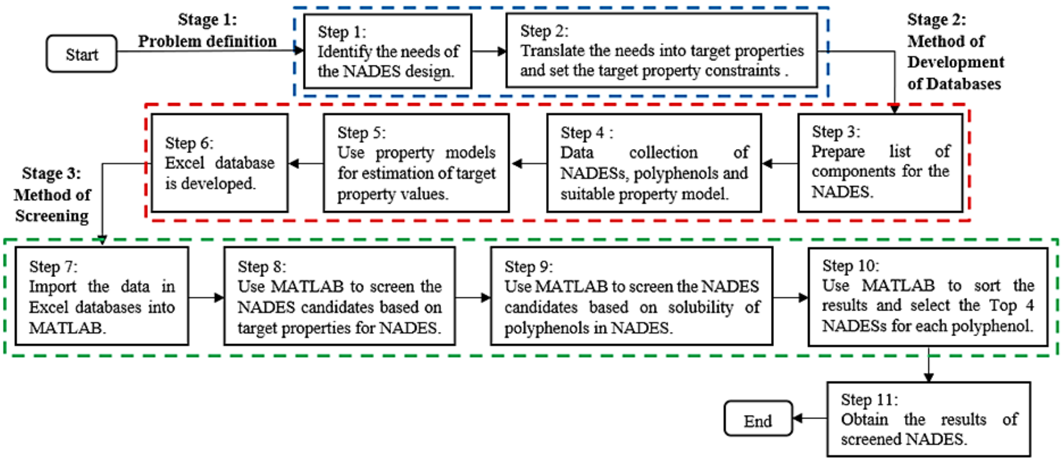

Figure 2: NADES design framework for user

3.1.1 Stage 1: Problem definition

Users are required to select their own needs for the NADES and translate the needs into compatible target properties. The target property constraints can be obtained from the related published study.

3.1.2 Stage 2: Method of development of databases

Users are requested to prepare the list of components for the combination of NADES. Data collection of NADES, polyphenols from jackfruit and property models were then performed from published literatures as this information are needed for screening process in stage 3. Property models were encouraged to be used for estimation of target property values.

3.1.3 Stage 3: Method of screening

Excel database which act as the input for framework should import into MATLAB by users. Then, users need to screen the NADES candidates based on each target properties for NADES. This is followed by second screening process which based on the solubility of polyphenols in NADES. The top 4 NADES which polyphenols can solubilize better in it were selected.

3.2 Case Study: NADES design for extraction of quercetin, artocarpin and gallic acid from jackfruit

The main objective of this case study was to show the detailed guideline by using the proposed framework. Quercetin presents in large amounts in both the jackfruit leaf and seed which can help to improve blood sugar control. Besides, artocarpin can be found in jackfruit wood which helps to slow the growth of bacteria and enhance the antimicrobial activities. According to the research conducted by Singh, it is showed that the flesh of jackfruit contains high amount of gallic acid (Singh et al., 2015). Due to these factors, quercetin and artocarpin were choose as the targeted flavonoids while gallic acid was choose as the targeted phenolic acid to be extracted out from jackfruit in this case study by following the research methodology in Figure 1.

3.2.1 Stage 1: Problem definition

According to the published studies, the requirements of NADES include thermally stable in liquid phase, not harmful to human being and environment, can flow smoothly without outside effort and has good solvation performance in extraction out the desired polyphenols. These criteria were translated into corresponding target properties and the constraints for target properties are obtained from literature search and by comparison with the commonly used solvents for extraction of polyphenols. The target properties identified were boiling point, toxicity, viscosity and solubility. The values for target properties can be predicted by using computational approach like COSMOtherm software or using mathematical model available in published literatures. Table 1 display the NADES design requirements and its constraints for each target properties.

Table 1: NADES design requirements and constraints

NADES design requirements	Target properties	Target values	Unit	Reference
Thermally stable to maintain in liquid phase	Boiling point, Tb	400 - 800	˚C	Mirza et al., 2015.
Not harmful to human being and environment	Toxicity, EC50	< 2.0	-	Rahman et al., 2017.
Not too sticky and can flow smoothly without outside effort	Viscosity, μ	< 6.0	cP	Troter et al., 2016.
Good solvation performance of polyphenols from jackfruit	Solubility, δ	Depend on targeted polyphenols	$\frac{\mathrm{g}\,(solute)}{\mathrm{g}\,(\mathrm{solution})}$	Sut et al., 2017.

3.2.2 Stage 2: Method of development of databases

As organic acid based NADES that obtained from published studies were utilized in this case study, components 1 of NADES that selected to be used were lactic acid, malic acid and citric acid while components 2 of NADES were consist of 17 different hydrogen bond acceptor group. This has successfully formed 51 possible combinations of NADES using MATLAB by inserting the HBA group and HBD group into the database. An extensive search on published literatures which related with the NADES experimental results were performed to obtain the molar ratio for NADES (Dai et al., 2013). Only 34 out of 51 NADES candidates can undergo the screening process while others were excluded due to missing data of molar ratio. TmoleX and COSMOtherm were used to estimate the selected target properties like boiling point and relative solubility while property models were used to predict the target property values of toxicity and viscosity. The databases must contain the physicochemical properties of NADES and polyphenols together with the corresponding parameters that used in each property model. Excel database was act as a “brain” in this research which provides input for the MATLAB software to execute the commands.

3.2.3 Stage 3: Method of screening

Screening process is required in order to reduce the NADES candidates according to the priority of the target properties by using MATLAB. 34 NADES candidates were first screened based on the boiling point. Then, toxicity was the second priority target property to screen the NADES candidates. This can ensure that green solvent which will not threaten human and environment can be achieved. Then it is followed by viscosity screening of NADES candidates. Lastly, NADES candidates are screened down by solubility value to ensure that they have good solvation performance for extraction of polyphenols from jackfruit. Top 4 NADES were selected for each polyphenol based on relative solubility value from the highest to lowest. It was clearly show that the numbers of NADES candidates were reduced based on the priority screening from 34 NADES candidates to 6 feasible candidates. Figure 3 exhibits the hierarchy of NADES screening process from stage 2 to stage 3.

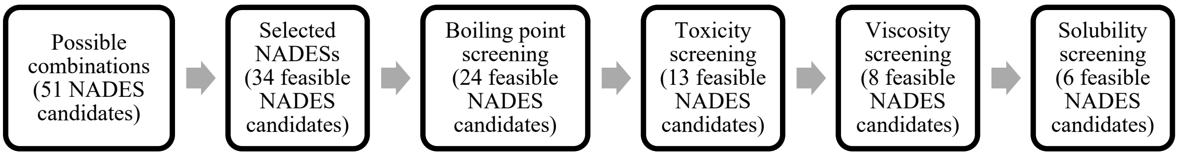

Figure 3: Hierarchy of NADES screening process

The results of NADES can exhibit in two aspects which are solvation performance and costing. The screened result of NADES candidates based on solubility of each polyphenol in NADES is shown in Figure 4. It is clearly showing that top 3 NADES for quercetin, artocarpin and gallic acid are exactly same which are NADES 33, 32 and 31. All their components consist of citric acid and L-proline but with different mole fraction. The only difference that can be observed based on Figure 4 is the fourth NADES which is NADES 27 for quercetin, NADES 19 for artocarpin and NADES 30 for gallic acid.

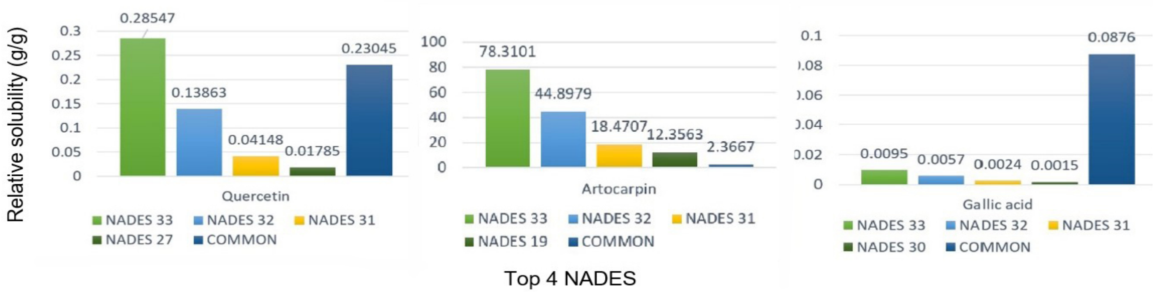

Figure 4: Top 4 NADES for each polyphenol with relative solubility value

From Figure 4, it is illustrated that NADES 33 can extract more quercetin than common organic solvent, ethanol while the others did not manage to do it. This situation happens most probably because of some NADES did not include in the screening process due to missing of data. There is possibility that the NADES that excluded has better solvation performance. For artocarpin, all the top 4 NADES has greater solvation performance compared to the ethanol. Moving on to gallic acid, Figure 4 exhibits that ethanol can extract more gallic acid than the top 4 NADES. The top 4 NADES for gallic acid have ordinary low relative solubility which means that they can only extract very limited amount of gallic acid from jackfruit. In this case, the components for NADES should have more variety rather than just use 3 components as HBD to form the combinations of NADES. By doing this, more possible combinations can be generated which can make the results more accurate. For this case, it obviously shows that the NADES available in the database did not have good solvation performance in extracting the gallic acid compared to the organic solvent based on Figure 4.
Table 2 shows the cost utilized for each NADES with their components and molar ratio.

Table 2: Cost utilized for each NADES

NADES	Components 1	Components 2	x1	x2	Cost (MYR)
NADES 33	Citric acid	L-Proline	0.25	0.75	468.00
NADES 32	Citric acid	L-Proline	0.33	0.67	427.19
NADES 31	Citric acid	L-Proline	0.50	0.50	340.46
NADES 27	Citric acid	Adonitol	0.50	0.50	1,502.27
NADES 19	Citric acid	D-Xylose	0.50	0.50	367.04
NADES 30	Citric acid	Ribitol	0.50	0.50	1,606.50
COMMON	Ethanol		1.00		241.55

Based on the comparison in term of costing, it shows that the cost that use NADES as extraction solvent are much higher rather than using ethanol as extraction solvent. Although the costing for NADES are higher than ethanol, but NADES still have its advantages as green solvents such as sustainability, biocompatibility and environmentally friendly. It depends on the person for their desired factors that they would like to consider with. For instance, if the company want to use the green solvent which will not harm the environment, they can have NADES as their option but if the company only have limited budgets on their projects, they still can choose to use organic solvent which are cheaper.

4. Conclusions

A NADES design framework for extraction of polyphenols from jackfruit has been developed. Computational approach was used to help for the prediction of the target property values, automatic calculation and screening of the results. Based on the framework, list of potential candidates of NADES were generated and selected for performance evaluation. According to the case study, NADES 33 was the best extraction solvent from current database which has the greatest performance as it has the greatest relative solubility in quercetin, artocarpin and gallic acid from jackfruit. As this research only covered the screening part, validation of the methods may be proceeding for future works. By doing this, the accuracy of the NADES selected can be known.

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