ABSTRACT

Objective: The aim of this study was to develop a more effective and environmentally friendly synthesis method for anti-cancer curcumin derivatives, namely 1,5-bis (4'-hydroxy-3'-metoxyfenyl)-1,4-pentadiene-3-one or gamavuton-0.

Methods: The experiment was conducted using two different energy sources, i.e. conventional heating and microwave irradiation. Vanillin and acetone were used as starting materials, and hydrochloric acid as the catalyst. During synthesis, variations in the synthesis period were carried out to study the effect of time on the gamavuton-0 produced. Based on experimental data, energy consumption between conventional method and microwave were evaluated.

Results: Evaluation of energy consumption was calculated based on experimental data. It was found that energy consumption for production using microwave irradiation was reduced to 0.0014 kWh/gram of crude gamavuton-0 products from 0.19 kWh/gram of crude gamavuton-0 product using conventional heating.

Conclusion: Based on calculations from experimental data, microwave irradiation during the synthesis of gamavuton-0 significantly saves energy consumption for synthesis.

Keywords: Cancer, Curcumin, Synthesis, Microwave, Energy savings

INTRODUCTION

In pharmaceutical chemistry, synthesis is commonly conducted for obtaining a new compound or a method for developing an established compound to better biological activity. Synthesis is usually conducted by combining two or more compound into more complex compound [1, 2]. Energy is usually required for the period of the synthesis. In this recent year, microwave are utilized for synthesis to replace the energy source. By applying this microwave, the synthesis was reported being more environmentally process, economical and new ways of improving green chemistry [3]. Numbers of researchers have been conducted many synthesis applying microwave irradiation as the energy source. The synthesis of dibenzylidenecyclohexanone derivatives via crossed Aldol Condensation was successfully conducted using the microwave for more environmentally production [4]. The synthesis of Pyrimidines assisted microwave was also successfully carried out with a good yield [5]. Synthesis for dibutyrylpyrimidinolone assisted microwave has been also developed as an efficient, green, cost-effective and eco-friendly synthesis method [6]. Some Schiff bases were synthesized in a very short time and excellent yield when the synthesis was conducted under microwave irradiation [7]. The phenyl acrylamide derivatives as potential active agent were also successfully synthesized under microwave irradiation [8]. Energy efficiency in the microwave-assisted solid-state synthesis of cobalt aluminate pigment was also calculated. It is reported that energy consumption was lower when the synthesis was conducted using microwave irradiation compared to conventional heating[9].

It is reported in the previous study, the curcumin derivative 1,5-bis (4'-hidroksi-3'-metoksifenil)-1,4-pentadien-3one or gamavuton-0 was synthesized in the round bottle flask using conventional heating (heating mantel). This method usually takes long time and consume a lot of energy to obtain the high yield [10]. Thus based on the previous work, this paper deals with the explanation of the effectiveness of gamavuton-0 synthesis using microwave irradiation compared to the conventional method.

MATERIALS AND METHODS

Materials

Starting material vanillin was obtained from Brataco® and acetone was obtained from Sigma Aldrich®. Hydrochloric acid as the catalyst was obtained from Merck® Germany and the eluent for the qualitative analysis i.e. chloroform and ethyl acetate were obtained from Sigma Aldrick®. Hydrochloric acid as the catalyst was added into acetone, separately. The hydrochloric acid that was added was 20 µl, thus the concentration of hydrochloric acid was 2 ppm. Further, 1 ml acetone was taken from the mixture of acid that was added was 20 µl, thus the concentration of hydrochloric acid was 2 ppm. Further, 1 ml acetone was taken from the mixture of acetone-hydrochloric acid and then added into dissolved vanillin in a round bottle flask that was prepared with the condenser. Heating at scale of 135 watt was set up. Cooling was done by turning on the water cooling through condenser. The duration of the reaction was stopped after 1, 2, 3, and 4 h respectively and the end of the reaction can be identified by forming a brownish yellow solution. The obtained solution was cooled in the refrigerator at 1-10 °C for 12 h. Purification was done by hot water maceration method. The yield was calculated by the weight of obtained crude gamavuton-0 produced divided by the weight of total starting material times100%. All the experiment was done for 3 times.

Synthesis of gamavuton-0 using conventional heating

Synthesis of gamavuton-0 was carried out in a round bottle flask with condenser by varying heating time (1, 2, 3, and 4 h, respectively) while keeping constant of heating level (4.5 scale = 135 watt) and ratio of vanillin and acetone (2:1). Vanillin that was used as much as 4.141 grams and acetone as much as 1 ml. Before reaction, Vanillin was dissolved in the ethanol 95% using a magnetic stirrer until dissolved. In the other hand, a designed value of concentrated hydrochloric acid (acid catalyst) was added into acetone, separately. The hydrochloric acid that was added was 20 µl, thus the concentration of hydrochloric acid was 2 ppm. Further, 1 ml acetone was taken from the mixture of acetone-hydrochloric acid and then added into dissolved vanillin in a round bottle flask that was prepared with the condenser. Heating at scale of 135 watt was set up. Cooling was done by turning on the water cooling through condenser. The duration of the reaction was stopped after 1, 2, 3, and 4 h respectively and the end of the reaction can be identified by forming a brownish yellow solution. The obtained solution was cooled in the refrigerator at 1-10 °C for 12 h. Purification was done by hot water maceration method. The yield was calculated by the weight of obtained crude gamavuton-0 produced divided by the weight of total starting material times100%. All the experiment was done for 3 times.

Synthesis of gamavuton-0 using microwave irradiation

Synthesis of gamavuton-0 using microwave irradiation was carried out in the porcelain evaporating disc under kitchen microwave irradiation. Vanillin and acetone were used as the raw materials and hydrochloric acid was used as the catalyst. First step of the synthesis was preparing of the raw material by weighing of 8.2 grams of vanillin and pipetting 2 ml of acidified acetone to meet the mole ratio of vanillin and acetone at 2:1. The concentration of catalyst that was used was 20 µl for 10 ml of acetone. The synthesis was conducted for 1, 2, 3, and 4 min with the power of microwave used at 400 watt. In the end of the synthesis, the gamavuton-0 inside the mixture was isolated using hot water...
The formamidin reaction results in the formation of disconnection analysis can be seen fig. 2. The synthesis of gamavuton-0 is initiated by analyzing of the formation of carbon-carbon (C-C) bonds. This reaction is very simple, environmentally friendly, and the raw materials are easily obtained [16].

RESULTS

Gamavuton-0 is reported by number of the researcher has many activities such as anticancer, anti-inflammatory, and anti-oxidants [12-14]. Gamavuton-0 is more stable compared to curcumine since this compound has a different middle chain, i.e. gamavuton-0 loss of methylene group and carbonyl group which is the main non stable group lead the degradation [15]. The chemical structure of curcumine and gamavuton-0 is illustrated in fig. 1.

In general, the synthesis of the curcumine derivatives is followed by the Claisen-Schmidt condensation reaction or the Aldol-Condensation of an aromatic ketone and aldehyde. The ketone acts as a nucleophile and the aromatic aldehyde acts as an electrophile. The Aldol-Condensation reaction is very popular and widely used in the formation of carbon-carbon (C-C) bonds. This reaction is very simple, environmentally friendly, and the raw materials are easily obtained [16].

The synthesis of gamavuton-0 is initiated by analyzing of the suitable raw material for synthesis. By using disconnection analysis, vanillin and acetone can be used as the starting material on gamavuton-0 synthesis. Theoretically, gamavuton-0 can be synthesized from 2 moles of vanillin and 1 mole of acetone. The result of disconnection analysis can be seen fig. 2.

In the effectiveness study of synthesis, two kind of experiments were conducted. First experiment was synthesis using conventional heating (heating mantel) as the energy source and the second experiment was synthesis using the microwave as the energy source. Both experiments were conducted in the different period of synthesis but at the same purification method (i.e. maceration) and the same ratio of starting material (4:1). The weight of the crude product after purification was determined and used to measure the yield of the gamavuton-0 produced. The experiments detail are as follow: the first experiment was conducted at this following condition: vanillin (4.1 grams): acetone (1 ml) = 4 moles: 1 mole; heating period = 1, 2, 3, and 4 h, respectively; and energy power = 135 watt. The second experiment was conducted at this following condition: vanillin (8.2 grams): acetone (2 ml) = 4 moles: 1 mole; irradiation period = 1, 2, 3, and 4 min, respectively; energy power = 400 watt. The crude gamavuton-0 produced from the both experiment are detailed in table 1 and table 2.

In the comparison of the both experiment, the longer time of synthesis was consumed and lower yield was collected when the synthesis was conducted using conventional heating (heating mantel) as the energy source. It can be seen in table 1 and 2, the highest yield of crude gamavuton-0 synthesized using microwave irradiation is 72.72% for 2 minute of reaction. Based on the data in table 1 and 2, the profile of the gamavuton-0 production can be expressed by grafted depicted in fig. 4 and Fig. 5. The trend of the gamavuton-0 production using heating mantel is increasing by the increase of time even though the reaction was done for 4 h. In comparison with the synthesis using microwave irradiation, the trend of the gamavuton-0 production seems following second-order reaction. There is an optimum irradiation time to obtain the maximum crude gamavuton-0 produced.
Table 1: The yield of gamavuton-0 crude product at different time of synthesis using microwave as the heating source

| Irradiation time (min) | Starting material (g) | Crude of gamavuton-0 (g) | Yield (%) |
|------------------------|-----------------------|--------------------------|-----------|
| 1                      | 9.78±0.010            | 4.84±0.076               | 49.49±0.74|
| 2                      | 9.79±0.011            | 7.12±0.016               | 72.72±0.061|
| 3                      | 9.79±0.006            | 6.76±0.189               | 69.05±1.888|
| 4                      | 9.77±0.010            | 6.69±0.087               | 68.47±0.793|

Note: weight of starting material = vanillin+acetone; all the data are presented as means±SD, n = 3.

Table 2: Crude gamavuton-0 produced at different time of synthesis using conventional heating

| Heating time (h) | Starting material (g) | Crude of gamavuton-0 (g) | Yield (%) |
|------------------|-----------------------|--------------------------|-----------|
| 1                | 4.89±0.021            | 2.53±0.221               | 51.73±4.510|
| 2                | 4.87±0.014            | 2.25±0.020               | 46.20±0.410|
| 3                | 4.88±0.007            | 2.51±0.100               | 51.43±2.053|
| 4                | 4.86±0.014            | 2.79±0.114               | 57.41±2.337|

Note: weight of starting material = vanillin+acetone; all the data are presented as means±SD, n = 3.

Fig. 4: The profile of gamavuton-0 production based on heating period using heating mantel as the energy source (means±SD, n = 3)

Fig. 5: The profile of gamavuton-0 production based on period using microwave irradiation of kitchen microwave as the energy source (means±SD, n = 3)

Based on the profile of gamavuton-0 production for both synthesis methods, the production rate of gamavuton-0 using microwave irradiation is found faster compared using heating mantel as the energy source for synthesis. Economics factor is often considered important during the selection of the reaction method rather than regulations, synthesis/treatment outcome, and operations (maintenance, control, safety) [18]. Since the both synthesis methods of gamavuton-0 is an electric-energy-intensive process and the electric energy can represent major consumption cost, hence the estimation of electrical energy demand is necessary.

A general and simple method for the evaluation of electrical energy for chemical reaction was proposed. The evaluation was conducted for the microwave-assisted solid-state synthesis of cobalt aluminate pigment. The energy efficiency is expressed as the ratio of the energy consumed and the weight of the product [9]. This proposed formula may be used for the gamavuton-0 synthesis. The specific energy consumed per gram crude gamavuton-0 produced can be seen in fig. 6. The evaluation was conducted for the highest yield for the both of synthesis method. It can be seen in fig. 6 that the specific energy consumption for synthesis using microwave was 0.0014 kWh/gram crude product and using heating mantel was 0.19 kWh/gram crude product.

Fig. 6: Specific energy consumption for synthesis of gamavuton-0 using different energy source

The data in fig. 6 show that the synthesis of gamavuton-0 assisted-microwave more efficient on saving energy and also more environmental friendly method compared to the synthesis using conventional heating. The same conclusion is also reported by Veronesi et al. [9] when synthesizing the solid-state synthesis of cobalt aluminate pigment and by Jaiswal and Dwivedi [19] when synthesizing antimicrobial aryl-triazole-1,3,4-thiadiazoles. The more efficient of synthesis using microwave irradiation may due to the thermal effect and non-thermal effects. The thermal effect are including the overheating, hot spots and selective heating, while the non-thermal effects may due to the highly polarizing field. This perhaps add the effects on the mobility and diffusion that may increase the probabilities of effective contacts of the starting material of the synthesis [20]. Thus, the microwave is a promising energy source for synthesis to replace the conventional energy.
source. This method has the advantage of being more environmentally process, economical and new ways of improving green chemistry [21].

CONCLUSION
Synthesis of gamavuton-0 was more effective conducted using microwave irradiation compared to conventional heating since the energy consumed during the synthesis was lesser when the synthesis using microwave irradiation.

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AUTHORS CONTRIBUTIONS
All the authors have contributed equally

CONFLICT OF INTERESTS
Declared none

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