

Cyperous Rotundus Active Compounds for Psoriasis Therapy with in Silico Analysis

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Abstract: *The choice of therapy in mild to moderate level of psoriasis includes topical therapy. In silico is an analog computerized experiment which is similar to in vivo and in vitro biological experiment. Cyperus rotundus or nut grass has antipsoriatic activity so that it can be used as a topical herbal medicine in reducing psoriasis severity. The aim of this study was intended to evaluate the content of Cyperus rotundus using in silico analysis in psoriasis treatment. Active compound of extracted Cyperus rotundus is taken from the knapsack database. Simplified Molecular Input Line Entry System (SMILE) format is taken from the pubchem database. The predictions on skin barrier repair, immunosuppressors, anti-inflammatory and antipruritic agents are performed by using a pass server. The molecular mechanism of active compounds in the human body is taken from the search tool for interacting chemicals (STITCH) which is experimentally predicted; then it is computationally analyzed. Further pathway analysis uses cytoscape software. There are 21 active compounds on Cyperus rotundus. The potential of Cyperus rotundus as immunosuppressor, anti-inflammatory, and antipruritic is predicted to have activity that is examined computationally, but this has not been proven in laboratory experiment or has small potential. The highest potential of Cyperus rotundus bioactivity in improving skin barrier which has the most function is beta-selinene with an average value of probable to be active (Pa) 0.715 predicted to have high potential computationally and laboratory tests. Overall, Cyperus rotundus is a good option for psoriasis therapy in improving skin barrier function, immunosuppressors, anti-inflammatory and antipruritic because it has beneficial effectiveness in terms of the availability and safety.*

Keywords: *Cyperus rotundus, In Silico, Psoriasis, immunosuppressors*

I. INTRODUCTION

Psoriasis is a disease characterized by abnormal proliferation of *keratinocytes* with skin manifestations in the form of well-demarcated *erythema* plaques accompanied by thick scales [1]. Some researchers mention immunological and genetic factors play a role in the etiology and pathogenesis of psoriasis [2]. The disorder is related to immune response, inflammation, cell proliferation, apoptosis and skin barrier function. Wolf et al reported that the damage to the integrity and the function of the skin barrier causes epidermal hyperplasia that leads to hyperproliferation in psoriasis [3].

The prevalence rate of psoriasis in the world reaches 2-3% of the total world population [4]. Epidemiological studies depict that there are differences in prevalence variables in different populations and ethnic groups around the world. The highest prevalence rate in western countries are in Norway as 4.5%, and in the UK as 2.2% [5]. The prevalence of psoriasis in America is reported to be 2.2%, and in Asia it is less than 0.3% [4], [6]. In Indonesia, according to the research of Winta et al, it is reported there are 198 psoriasis cases (0.97%) in RSUP Dr. Kariadi Semarang for a span of 5 years (2003-2007) [7]. Data obtained from RSUD Dr. Moewardi Surakarta from January 2012 to December 2016 by Wirawan et al shows the incidence of psoriasis that reaches 4.5% [8].

The accuracy in diagnosing and choosing the therapy in the therapy management of psoriasis can affect the quality of life for psoriasis sufferers. The severity of the disease can help to guide the therapy management. A therapy option for mild to moderate levels of psoriasis, one of them, is topical therapy. Severe psoriasis requires therapies, among others are phototherapy, acitretin, methotrexate, cyclosporine or biological therapy [9]. In the world population, there are 80% of psoriasis sufferers with mild degrees who are treated with topical therapy [10].

In silico is an analog computational experiment which involves biological experiments *in vivo* and *in vitro*. In *in silico*, there is an analytical description of the potential for active compounds chemically, biologically and pharmacologically. This information can be used in the creation of computational models or simulations to make predictions, suggest hypotheses and provide discoveries or advances in medicine and be used for therapy [11]. It is currently available of data that is more than 60 million organic compounds which have been synthesized as samples for biological activity testing [12].

Herbal medicine is the oldest medicine known to man and is still the most widely used drug in the world. World Health Organization (WHO) estimates that about 80% of the world's population uses traditional medicinal plants derived from plants [12]. *Cyperus rotundus*, also known as nut grass, is an herbal plant that has topical effects as anti-psoriasis, anti-inflammatory, antioxidant, anti-cancer and others [12], [13]. Reference [13] shows that the flavonoid content in *Cyperus rotundus* shows antipsoriatic activity so that it can be used as an herbal medicine to reduce the severity of psoriasis. This study aims to evaluate computationally in determining the potential of active compounds and the potential of biological activity of *Cyperus rotundus* which plays a role in the treatment of psoriasis.

II. METHODS

This research is descriptive analytic with *in-silico* analysis method. The assessment was carried out at Bioinformatics and Biomolecular Biology Laboratory, Brawijaya University, Malang.

A. Analysis of the Compound of *Cyperus Rotundus* or Nut Grass.

The *Cyperus rotundus* compound analysis was done by downloading KNApSACk website (http://kanaya.naist.jp/knapsack_jsp/top.html) ; then, the searching was done with the keyword *Cyperus rotundus*. *Cyperus rotundus* was found contains 21 potential compounds, namely *trans-calamenene*, *myrtenol*, *α -selinene*, *cyperolone*, *rotundenol*, *alloaromadendrene*, *gamma-muurolene*, *nootkatene*, *α -cyperone*, *isocyperol*, *cyperol*, *kobusone*, *isokobusone*, *beta-selinone*, *caryophyllene*, *trans-pinocarveol*, *limonene*, *beta-pinene*, *spathulenol* [14]-[18].

B. Analysis of the Potential Prediction of *Cyperus Rotundus* Compounds

The analysis data of *Cyperus rotundus* was obtained from Prediction of Activity Spectra for biologically active Substances (PASS) server/prediction by downloading PASS Online website (<http://www.pharmaexpert.ru/passonline>) The analysis used Structure Activity Relationship (SAR) approach. The active compound of *Cyperus rotundus* was extracted from the *knapsack* database with Simplified Molecular Input Line Entry system (SMILE) format taken from the *pubchem* database.

C. Analysis of the Potential Bioactivity of Active Compounds in *Cyperus Rotundus*

Prediction analysis of *Cyperus rotundus* in repairing the skin barrier, immunosuppressor, anti-inflammatory and anti-pruritic was done using *pass server*. The molecular mechanism of active compounds in the human body was taken from Search Tool for Interacting Chemicals (STITCH) which was experimentally predicted; then, it was analyzed computationally. Further pathway analysis used *cytoscape* software.

The potential of *Cyperus rotundus* was reviewed based on the predicted *probable to be active* (Pa) value with *Way2Drug PASS* server. Pa value is a value that describes the potential of a compound being tested. Assessment of Pa value ≥ 0.7 indicates that the compound is predicted to have a computationally high potential and also a high potential in laboratory tests. A Pa value of 0.3-0.7 means that the compound computationally has the ability to perform the activity being tested, but in laboratory tests it has not been proven or it has little potential. The value of Pa ≤ 0.3 means that the compound has low potential computationally, and it also has low potential in laboratory tests.

III. RESULTS

This research used *in silico* analysis method to analyze potential active compounds and to assess the bioactivity potential of *Cyperus rotundus* [Fig. 1]. The results of the analysis of the active compound of *Cyperus rotundus* can be seen in [Table 1], of the 21 potential active compounds that have a role in improving skin barrier function, immunosuppressors, anti-psoriasis, anti-inflammatory, and anti-pruritic properties.

Table 1. *In Silico* Analysis of Active Compounds on *Cyperus rotundus*

Active Compounds	Repair of skin barrier function	Immunosuppressors	Anti-inflammatory	Antipruritus
<i>Trans-calamenene</i>	-	0.612	0.71	0.607
<i>Myrtenol</i>	-	-	0.716	-
<i>α-Selinene</i>	0.787	0.722	0.705	0.373
<i>Cyperolone</i>	0.727	0.62	0.408	0.376
<i>Rotundenol</i>	0.712	0.631	0.26	0.55
<i>Alloaromadendrene</i>	0.861	0.698	0.318	0.345
<i>Gamma-Muuroleone</i>	0.718	0.654	0.64	0.507
<i>Nootkatene</i>	0.733	0.623	0.485	0.353
<i>α-cyperone</i>	0.785	0.699	0.502	0.311
<i>Isocyperol</i>	0.855	0.789	0.697	0.608
<i>Cyperol</i>	0.77	0.742	0.459	0.36
<i>Kobusone</i>	0.573	0.637	0.746	0.337
<i>Isokobusone</i>	0.706	0.648	0.714	0.581
<i>Rhamnetin</i>	0.277	0.653	0.732	0.339
<i>Beta-Selinene</i>	0.894	0.782	0.764	0.537
<i>Solavetivone</i>	0.613	0.787	0.292	0.317
<i>Caryophyllene</i>	0.734	0.626	0.745	0.442
<i>Trans-Pinocarveol</i>	0.684	0.498	0.491	0.616
<i>Limonene</i>	0.715	0.714	0.606	0.319
<i>Beta-Pinene</i>	0.709	0.511	0.601	0.514
<i>Spathulenol</i>	0.749	0.713	0.521	0.352
Pa Average	0.715	0.667	0.576	0.432

The function of *Cyperus rotundus* as an immunosuppressor with the most important role is *isocyperol* with an average Pa value of 0.667. The most potent anti-inflammatory role is *beta-selinene* with an average Pa value of 0.576. The potential of the active compound of *Cyperus rotundus* as an antipruritic, the most important role is *trans-pinocarveol* with an average Pa value of 0.432. The potential of *Cyperus rotundus* as an immunosuppressor, anti-inflammatory and anti-pruritus was computationally predicted to have the ability to activity being tested, but the laboratory tests have not been proven or they still have small potentials. The highest bioactivity potential of the active compound of *Cyperus rotundus* is in improving the function of the skin barrier, the most important role is *beta-selinene* with an average Pa value of 0.715 which is predicted to have high potential computationally and also in laboratory tests.

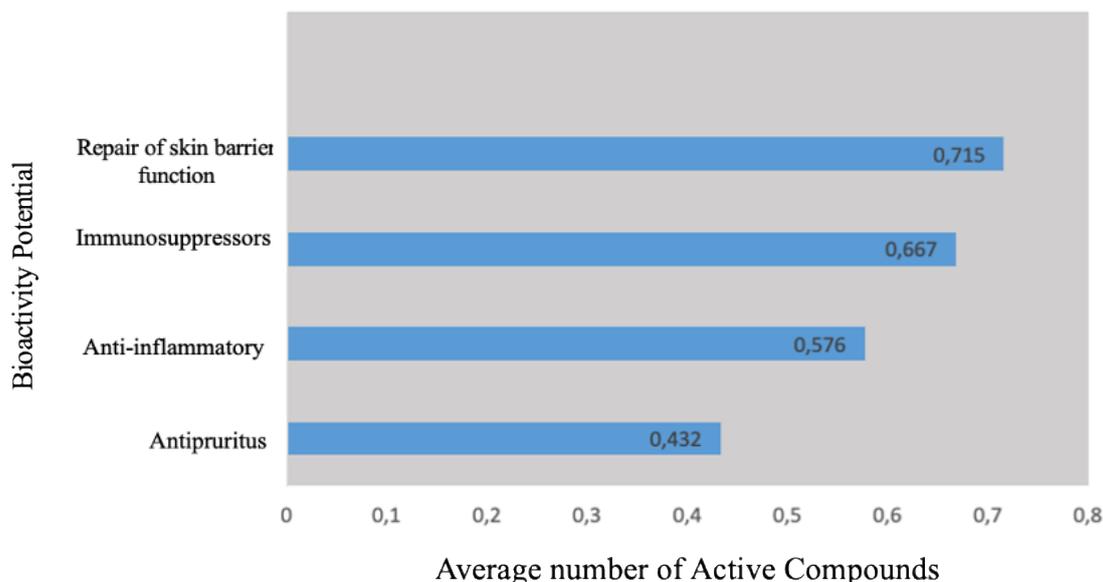


Fig. 1 Bioactivity potential of active compounds on *Cyperus rotundus* by *in silico* method

IV. DISCUSSION

Experimental testing of tens of millions of organic compounds for thousands of biological activities is difficult, so computational methods are needed to find and optimize new pharmacologically active compounds. The computational approaches are currently used for drug discovery and they are divided into structure-based drug designs and ligand-based drug designs. The discovery of new active compounds for pharmacology involves several specific activity criteria, in which these compounds have side effects and minimal toxic properties with appropriate pharmacological characteristics [12]. An experimental study was conducted by Ravi et al. used *in silico* method by analyzing *centella asiatica* and *indigofera aspalathoides* which role as antioxidants in psoriasis therapy [19].

Cyperus rotundus or nut grass is a family of *cyperaceae*, *Cyperus* class and species of *rotundus*. *Cyperus rotundus* morphology is a round tuber, measuring 1 to 3.5 cm, white in color that turns brown and hard with age. Triangular grass stems with a height of 30-40 cm. The leaves are green, glossy, 20 to 30 cm long and 0.2 to 1 cm wide. The flower is located at the tip of the stem, reddish brown or purple. *Cyperus rotundus* is a weed that can be found in tropical, subtropical and temperate regions of the world [14].



rotundus contains 52 (9.07%), *trans-* that *Cyperus*, anticancer and

Fig. 2 *Cyperus rotundus* [21]

Psoriasis is characterized by inflammation and hyperproliferation of the epidermis. Cells in the epidermis divide faster than the normal ones, causing damage to the skin barrier. Under normal circumstances, the skin acts as a protector so that the damaged skin barrier will be more susceptible to infection and dehydration [22]. Since 2 decades ago, Williams and Elias reported that in psoriasis there is a disturbance in the integrity and the function of the skin barrier which functions in the regulation of DNA synthesis in the epidermis. This disturbance generates a signal to the nucleus in the epidermis to produce excessive cells and body lamellar causing hyperplasia of the epidermis as compensation for repairing the skin barrier [3]. In this study *Cyperus rotundus* has the potential of bioactivity in repairing the skin barrier (Pa: 0.715) which is computationally high, and also in the laboratory tests. This is because *Cyperus rotundus* contains beta-selinene in repairing the skin barrier which functions as protection for DNA damage in the epidermis [23].

For more than 25 years, interleukin (IL)-6 has been linked to the pathogenesis of psoriasis. Interleukin-6 is produced by keratinocytes, fibroblasts, endothelial cells, dendritic cells, macrophages and T helper type 17 cells [24]. Interlukin-6 is a proinflammatory cytokine that involves in many physiological and pathological processes by integrating with several intracellular signaling pathways. Deviated IL-6 expression was associated with growth, metastasis and chemotherapy resistance in cancer. Interlukin-6 has an immunosuppressive function by stimulating the infiltration of suppressor cells [25]. In this study, *Cyperus rotundus* has the potential for immunosuppressor bioactivity (Pa: 0.667) with computationally predicted of having the ability on the activity which is being tested, but laboratory tests have not been proven or have little potential. This is because *Cyperus rotundus* contains *isocyperol* which can significantly inhibit IL-6 content [26].

In *psoriasis* there is inflammation of the skin caused by many immune cells that produce cytokines, chemokines and inflammatory molecules [22]. Inflammation causes cell migration, plasma exudation and the production of mediators such as nitric oxide, prostaglandin E₂, IL-1 β , IL-6 and tumor necrosis factor (TNF)- α which is able to attract leukocytes such as neutrophils [27]. Studies by Richa et al using gas chromatography mass spectrometry (GC-MS) analysis reported that *Cyperus rotundus* contains beta-selinene which has anti-inflammatory activity [28]. In this study, *Cyperus rotundus* has the bioactivity of anti-inflammatory potential (Pa: 0.576) with computational prediction that has the ability on the activity being tested, but laboratory tests have not been proven or have little potential. This is because *Cyperus rotundus* contains beta-selinene as anti-inflammatory which functions to inhibit the synthesis of inflammatory mediators involved in cell migration [27].

Various studies over the past 30 years have documented that *pruritus* is a common phenomenon of clinical symptoms of psoriasis affecting the majority of patients analyzed [29]. The pathogenesis of pruritus in psoriasis is the presence of neurological disorders and neuropeptide imbalance. Pruritus is induced by an increase in IL-2 expression, vascular disorders, the opioid system, prostanoids, IL-31, serotonin or proteases [30]. The study by Al-Snafi reported that *Cyperus rotundus* contains trans-pinocarveol compounds [20]. In this study, *Cyperus rotundus* has the bioactivity potential as an antipruritic (Pa: 0.432) with computational prediction that has the ability on the activity being tested, but laboratory tests have not been proven or have little potential. This is because *Cyperus rotundus* contains *trans-pinocarveol* as an antipruritic which functions to inhibit serotonin [31].

V. CONCLUSION

Through *in silico* analysis, *Cyperus rotundus* contains 21 active compounds. *Cyperus rotundus* immunosuppressor, anti-inflammatory and antipruritic are computationally predicted to have the ability on the activity being tested, but laboratory tests have not been proven or have little potential. The highest bioactivity potential of the active compound of *Cyperus rotundus* is to improve the function of the skin barrier, the active compound that plays the most role is beta-selinene which is predicted to have a computationally high potential and in the laboratory tests. *Cyperus rotundus* is a good option for topical treatment of psoriasis because of its beneficial effectiveness in terms of availability and safety.

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