The Novel Postpartum Herbal Drugs: An *in Silico* Approach of Bakumpai Dayak Tribe Traditional Medicinal Plants

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Abstract. The postpartum mother is primarily when she gets an infection (puerperal) of the genital tract caused by anaerobic microorganisms and pathogenic aerobes including *Streptococcus*. The Central Kalimantan people, especially the Bakumpai Dayak tribe, still rely on the forest potential as medical needs by using the term "tatamba kampung/traditional healing" where the process of gathering, processing, and its use is done traditionally. This study aimed at predicting what types of compounds available in bio herbal postpartum drugs based on bioinformatics studies. The study was conducted by modeling the compound 3D structure using the PubChem database. The 3D structure and bioactive potential used PASS-server Way2Drug method, Swiss Target Prediction. A typical Bio herbal of Bakumpai Dayak tribe has been proven to have an antimicrobial compound for postpartum. However, bioactive compounds from *Curcuma domestica* Val, *Parkia roxburghii* G.Don, *Eclipta alba* L, *Citrus aurantifolia*, *Ageratum conyzoides* L, *Callicarpa logifolia* Lamk, *Alium sativa* L., and *Marus alba* L. were more effective as antifungal, and *Gradema agusta* Merr had the highest potential antifungal of computation (0.639) compared to other bio herbals.

Keywords: Postpartum, herbal drugs, Bakumpai Dayak tribe, in Silico

1. Introduction

*Postpartum* is maternal morbidity and mortality post childbirth or the baby born in particular after the placenta is released from the uterus (6-8 weeks post-baby delivery) [1]. During the postpartum period, women generally will develop to the inflammation stage due to postpartum infection (puerperal) in the genital tract caused by the aerobic and anaerobic microorganisms pathogens infection [2-3]. Specifically, postpartum occurs 28 days after the baby is born. *Postpartum/puerperal* infection is characterized by the increase in body temperature up to 38 °C, and it requires a specific treatment against this medical problem [4].

Importantly, the people of Central Kalimantan, especially the Bakumpai Dayak tribe community, still depend on the potential resources of the forest [5]. The community collects various types of forest products, then uses them as a primary source of their daily needs, such as for cloth, food, and community health [6]. The Bakumpai Dayak community depends on the natural herbs for healthcare by using the local biodiversity as traditional medicine, including for the reproductive health after childbirth (*postpartum*). The previous ethnobotany study proved that the Central Kalimantan Dayak tribe community is the most significant community who is using natural materials to fulfill their health...
needs (80.7%) compared to other regions in Indonesia. Interestingly, the floodgates of traditional commercial products to the Malaysian market have been out of control since 2017 [7].

The natural ingredients for health treatment by Dayak Bakumpai tribe in Central Kalimantan are commonly known as “tatamba kampung”. This traditional method was inherited from the previous generation, and this cultural property should be preserved [8]. Tatamba kampung is a unique treatment by utilizing a particular part of traditional plants, which are accompanied by specific technique and rituals [9-10,12]. The Dayak Bakumpai Tribe believes that there is a lot of plants around them that can be used as medicine, especially for post-partum infection [11]. In their perspective, the local wisdom is not only for the spiritual tradition of the Dayak Bakumpai Tribe of Central Kalimantan, but also offers the beneficial for healthcare [12]. In line with the Bakumpai Dayak Tribe, the previous report showed that ethnopharmacological data were used to link modern traditional medicine and epidemiological data that act as evolutionary medicine [13]. Hence, the primary screening of potential traditional Dayak Bakumbai medicinal plant is required as the preliminary scientific investigation.

According to the Dayak Bakumpai Tribe data, there are 9 types of potential medicinal plants for postpartum treatment, such as Janar (Curcuma domestica Val), Kedaung (Parkia roxburghii G.Don), Fatimah Grass (Eclipta alba L.), Sangkareho (Callicarpa logifolia Lamk), Kaca Piring (Gradema agusta Merr), Lime (Citrus aurantifolia), Tambora (Ageratum conyzoides L), Keratau (Marus alba L.), and Garlic (Allium sativa L.) [6]. All those plants are easy to grow in Kalimantan [5-6]; however, the limited scientific information of the potential medicinal properties for each species remains. This study aimed to analyze the possible natural ingredients within the local medicinal plants of Dayak Bakumpai by in silico model based on a bioinformatics approach.

2. Methods
The research was carried out by predicting bioactive potentials compounds in medicinal plants using the PASS Prediction-Way2 Drug server (http://www.phamexpert.ru/passonline) Swiss Target Prediction (http://swissmodel.expasy.org/). The interaction between bioactive and essential proteins against microbes was analyzed using the STICH web server (http://stitch.embl.de/egi/showpage.pl) and STRING (http://string-db.org/).

3. Results and Discussion
The results of the study showed that the plants used by the Bakumpai Dayak Tribe in Central Kalimantan as an infectious drug at postpartum were proven to have antimicrobial compounds that caused the infection. PASS prediction was conducted to determine the biological activity of active ingredients from Janar (Curcuma domestica Val), Kedaung (Parkia roxburghii G.Don), Fatimah grass (Eclipta alba L.), Sangkareho (Callicarpa Longifolia Lamk), Kaca Piring (Gardenia jasminoides Merr), Lime (Citrus aurantifolia), Tambora (Ageratum conyzoides L), Keratau (Marus alba L.), and Garlic (Allium sativa L.). The activities tested were anti-bacterial, anti-fungal, Antiseptics, and antibiotics. The potential of plants as antimicrobials was reviewed based on Pa (probability to be active) predicted by the Way2Drug PASS server.

Pa (probability to be active) value is a value that describes the potential of a compound that is tested as antimicrobial. If the value is 0.3 > Pa < 0.7 then the compound is computationally predicted to have potential as antimicrobials, but not yet certain in oratorical lab testing. Whereas, if the Pa > 0.7 then the compound is predicted to have high potential as an antimicrobial, both in the way of computing and testing in the laboratory. To obtain the potential predictions value, the analysis was carried out computationally. The basic data proved that all plants had antibacterial, antifungal, and antiseptic properties. However, Curcuma domestica Val., Eclipta alba L., Citrus aurantifolia, and Ageratum conyzoides L., had no potential as an antibiotic. Furthermore, Parkia roxburghii, Callicarpa logifolia Lamk, Gradema agusta Merr, Marus alba L., and Allium sativa L. had the potential activity as antibacterial agent, antifungal, and antiseptic as shown in Table 1.
Based on Table 1, the potential of bioactive compounds in the plants was tested. Overall, the plants used by the Bakumpai Dayak people in Central Kalimantan were in the range of 0.3 > Pa < 0.7 so that the potential of these compounds still required an experimental lab, even though their computational potential had been proven as antimicrobial, antifungal, and Antiseptic. The Pa <0.3 computationally (Table 1) illustrated that the *Curcuma domestica* Val, *Parkia roxburghii* G.Don, *Eclipta alba* L., *Citrus aurantifolia*, *Ageratum conyzoides*, *Callicarpa logifolia* Lamk, *Allium sativa* L., and *Marus alba* L. was considered more effective as antifungal where *Gradema agusta* Merr. had the highest computational antifungal potential (0.64) compared to other plants.

The effectiveness of bioactive compounds in plants that have the potential as antifungals was then computationally analyzed to see the interactions between bioactive and essential proteins to fungi. Based on the results of predictive analysis of protein interactions using STITCH, several active compounds from *Curcuma domestica* Val, *Parkia roxburghii* G.Don, *Eclipta alba* L., *Callicarpa logifolia* Lamk, *Gradema agusta* Merr, *Citrus aurantifolia*, *Ageratum conyzoides* L., *Marus alba* L., and *Allium sativa* L could interact with ergosterol biosynthesis protein through several protein intermediaries. Some proteins passed as intermediary interactions are shown in Table 2.

Based on Table 2, the protein used as an intermediary for biosynthetic interactions with the varied average shortest path length (Figure 1). This analysis indicated that bioactive compound on plants would interact with proteins SW16, ERG11 and NCP1. That protein is a protein that plays a role in ergosterol biosynthesis and UPC2 as biosynthetic control, where it is known that ergosterol is a component in the cell membrane of the group yeast [2]. Ergosterol (ergosta-5,7,22-trien-3β-ol) is the sterol fat found in the fungi membranes cell that functions like cholesterol in animals [14,15]. Sterols can be found as free sterols, sterol esters, sterol alkyl ethers, sterol sulfates, and sterol glycosides which can then be acylated to yield sterol glycosides. The analysis of interactions between bioactive and essential proteins for fungi or yeasts is shown in Table 3.

Bioactive compounds in plants will interact with proteins SW16, ERG11, and NCP1. The protein plays a role in ergosterol biosynthesis, wherein SW16 can inhibit the expression of NCP1 and ERG11, and UPC2 acts as a control of ergosterol synthesis protein and is also involved in the integrity of cell wall of fungal hyphae [2]. In connection with the protein role in the biosynthesis of ergosterol, the ergosterol is very important for fungi as an enzyme and is one part of the steroids [16]. Steroids in plants, animals, and humans, and low-level organisms vary. Steroids in plants are known as phytosterols; in animals and human, it is cholesterol, whereas in the group of fungi called with ergosterol [17]. Ergosterol is a molecule smaller than lanosterol; ergosterol was synthesized by a combination of two farnesyl pyrophosphate molecules, along with terpenoids -15-carbon, into lanosterol, which has 30 carbons. Then, two methyl groups were removed, forming ergosterol [18].

| Species                        | Antibacterial | Antifungal | Antiseptic |
|-------------------------------|---------------|------------|------------|
| Kunyit (*Curcuma domestica* Val) | 0.41          | 0.50       | 0.46       |
| Keduau (*Parkia roxburghii*)  | 0.35          | 0.50       | 0.35       |
| Rumput Fatimah (*Eclipta alba* L.) | 0.50          | 0.57       | 0.60       |
| Jeruk Nipis (*Citrus aurantifolia* L.) | 0.40          | 0.52       | 0.40       |
| Tambora (*Ageratum conyzoides* L.) | 0.27          | 0.32       | 0.32       |
| Bawang Putih (*Allium sativa* L.) | 0.35          | 0.54       | 0.23       |
| Sangkarehoh (*Callicarpa longifolia* Lamk) | 0.38          | 0.43       | 0.19       |
| Keratau (*Marus alba* L.)     | 0.43          | 0.55       | 0.36       |
| Kaca Piring (*Gardenia jasminoides*) | 0.54          | 0.64       | 0.31       |

Table 1. The characterization of potential predictive value from Dayak Bakumbai Medicinal Plants
Table 2. Biosynthesis interaction protein intermediate

| No. | Protein | Average shortest path length | Between Centrality |
|-----|---------|------------------------------|--------------------|
| 1   | CLB2    | 3.17                         |                    |
| 2   | CLB1    | 3.17                         |                    |
| 3   | ERG24   | 2.92                         |                    |
| 4   | ERG11   | 2.85                         |                    |
| 5   | CLB3    | 3.17                         |                    |
| 6   | CDC28   | 3.17                         |                    |
| 7   | ERG25   | 2.92                         |                    |
| 8   | CLB4    | 3.17                         |                    |
| 9   | ERG26   | 2.92                         |                    |
| 10  | CEF1    | 3.58                         |                    |
| 11  | PRP8    | 3.73                         |                    |
| 12  | CLB5    | 3.17                         |                    |
| 13  | ERG7    | 2.94                         |                    |
| 14  | ERG27   | 2.92                         |                    |
| 15  | SWI6    | 2.42                         | 0.61               |
| 16  | ERG2    | 2.89                         |                    |
| 17  | ERG6    | 3.56                         |                    |
| 18  | ERG28   | 3.58                         |                    |
| 19  | UPC2    | 3.39                         |                    |
| 20  | ECM22   | 3.42                         |                    |
| 21  | NCP1    | 2.38                         | 0.60               |
| 22  | MOT3    | 3.77                         |                    |

The position of ergosterol in the fungal cell membrane caused ergosterol to play an essential role as a target receptor for the treatment of infections caused by fungi, and as a target of various drugs [19]. Ergosterol in cell membranes forms polar pore fungus creating the ions (predominantly potassium and protons). Furthermore, other molecules can leak out, which will kill the cells. In other cases, bacteria or fungi can also avoid macrophages by utilizing the protein [2,19]. In the postpartum period, women are very susceptible to vaginal fungi infection, including *Candida albicans* (vaginal candidiasis) [20]. This condition is related to postpartum hormones. Ergosterol, cholesterol, progesterone, and estrogen are compounds derived from steroids. Estrogen is a substrate for the development of *Candida albicans* in the vagina. The increasing levels of estrogen have a positive effect on increasing vaginal candidiasis. Other diseases are caused by *Candida albicans* [21-22]. Importantly, the colonization of *Candida albicans* on the mucosal surface during or immediately after birth will increase a high risk of endogenous infection [23].
Table 3. The analysis of proteins that contribute as antifungal

| Compound               | Protein | Interaction | Biological Process                        | Information                                                                 |
|------------------------|---------|-------------|-------------------------------------------|----------------------------------------------------------------------------|
| Allicin and eugenol    | SWI6    | Direct – Activation | cellular biosynthesis                      | Interact with NCP1, ERG27, ERG7, ERG11, ERG28, ERG26, ERG24, ERG2, ERG6, MOT3, ECM22 to UPC2 |
|                        |         |             | Ergosterol biosynthesis, steroids biosynthesis, | Interact with ERG27, ERG7, ERG25, ERG11, ERG28, ERG26, ERG24, ERG2, ERG6 to go to UPC2. |
| Catechin and genipin   | NCP1    | Direct-binding | Cellular biosynthesis                      | Interact with ERG27, ERG7, ERG11, ERG28, ERG26, ERG24, ERG2, ERG6, MOT3, ECM22 to UPC2 |
|                        |         |             | Metabolic cellular lipids                 | Interact with ERG27, ERG7, ERG11, ERG28, ERG26, ERG24, ERG2, ERG6 to go to UPC2. |
| Nobiletin              | ERG11   | Direct      | Ergosterol biosynthesis, steroid biosynthesis | Interact with ERG27, ERG7, ERG25, ERG28, ERG26, ERG24, ERG2, ERG6 to get to UPC2. |
|                        |         |             | Cellular biosynthesis                      | Interact with ERG27, ERG7, ERG28, ERG26, ERG24, ERG2, ERG6, MOT3, ECM22 to get to UPC2. |
|                        |         |             | Metabolic cellular lipids                 | Interact with ERG27, ERG7, ERG28, ERG26, ERG24, ERG2, ERG6 to get to UPC2. |

Estrogen hormone causes some biological effects on target organs [24]. It can stimulate follicular growth in ovarian, the growth of the endometrium in the uterus causes cornification or silting of epithelial cells in the vagina. As a consequence, it will increase the mucus secretion and reduce the thickness of mucus in cervix results in the release of gonadotropins in the pituitary gland [24-25]. The binding of estrogen with typical receptors in the cytoplasm or outside the nucleus protein causes the changes in the conformational form of the protein, thus facilitating the penetration of the estrogen-receptor complex into the cell nucleus. The complex then binds the acceptor in the chromosome, triggers mRNA and protein synthesis, thereby enhances the growth and development of the reproductive tract tissues [23].

Several species of the candida yeast genus can cause candidiasis [26]. Candida species are easily found in the digestive tract, mucous membranes, and the normal flora of the skin. Candida species that colonize in the mucosal surface during or immediately after birth induce the higher incident of endogenous infection and systemic mycosis [27]. Also, in this study, it was analyzed the basic pathway of *postpartum* infection involving ergosterol and fungi by using bioinformatics analysis. The
preliminary data of the value of a leverage shortest path length analysis are shown in Table 3. The prediction mechanism is an analysis to find out the fastest path of a network pathway. Importantly, NCP1 and SWI6 protein are predicted to be the fastest intermediate protein pathway to interact with the other target protein [1]. The web server used in this study has not found the data of bioactive interaction and ergosterol essential protein that involves Candida albicans (Figure 1).

**Figure 1.** Analysis of bioactive interaction and ergosterol essential protein against infection

The medicinal plants used by the Bakumpai Dayak tribe in Central Kalimantan based on bioinformatic analysis contain compounds belonging to the derivatives of alkaloids, flavonoids, saponins, and tannins. It is known that some steroid sapogenins such as diosgenin function as precursors for sex hormones. The isomers are Yamogenin, gitogenin, tigogenin, and trigoneoside saponins (like estrogen); they have effects as phytoestrogens for pre-menopausal therapy. The host microenvironment involves regulation and adaptation from both of the commensal and pathogenic states [27]. The pathogenic potential can be upregulated to subvert immune surveillance or downregulated to sustain commensalism [6]. The cell membrane of fungi contains plant sterols [28] whereas this sterol is a critical component related to its integrity. The use of synthetic drugs or antibiotics as antifungal treatment method induce not only fungi cell death, but also a little bit harms for human tissue [23]. Advanced biotechnology was by increasing bioactivity in building biological systems to find new drugs. Mushrooms and yeast increase antibacterial production as well as pharmacological activities in Biological biosafety enhancement [29]. Instead, using natural materials as a shade only targets specific pathways or processes for fungal cells, thereby reducing the possibility of damaging the tissue. The mechanisms of action of antifungals are fungicidal and fungistatic. The previous studies suggested that stress responses are essential mediators of resistance to diverse antifungals [30]. Fungicidal as a compound that can kill fungi, while fungistatic can inhibit the growth of fungi without turning it off. Candida albicans is a pathogen from immunocompromised [28], and there are other inhibiting factors such as Tricyclic antidepressants that inhibit Candida albicans growth and biofilm formation [31]. Also, Cinnamaldehyde demonstrated particular efficacy on 1,3-β-D-glucans in the cell wall of C. albicans [32].

The mechanism of action of antifungal compounds could occur by destroying the cell wall of fungi [33]. The fungal cells wall does not contain peptidoglycan, β-lactams or glycopeptides which are the
target of antibiotic action [14]. However, the cell wall of the fungi is a multilayer structure which consists of three main components, chitin, glucans, and mannanproteins. These components are served as antifungal action targets. In addition to damage cell walls, the mechanism of compounds in natural materials could also damage cell membranes [35]. Mannoprotein is the most significant component of fungi cell membrane and showed a change as the antifungal target. It will result in permeability of cell membranes, interaction with ergosterol. The formation of complexes with ergosterol in the fungal cell membrane could cause membrane damage and leakage [2,36].

4. Conclusion
Bioactive on Curcuma domestica Val, Parkia Roxburghii G Don, Eclipta alba L., Citrus aurantifolia, Ageratum conyzoides L., Callicarpa longifolia Lamk, Allium sativa L., and Marus alba L. plants could be proposed as an antifungal agent. Gardenia jasminoides Merr had the highest potential of antifungal compared to the other herbs. Allicin, eugenol, catechin nobiletin, and genipin are bioactive in these plants which can interact with the essential protein ergosterol in fungi. Also, NCP1 and SW16 were predicted to be the fastest pathway from bioactive network pathway to interact with UPC2 multiple targets.

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