RESEARCH PAPER

Analysis of the Role of Ulva Lactuca Bioactive Compounds from Gondol Beach Bali as an Antioxidant and Anti-Infertility

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ABSTRACT
Ulva lactuca algae are one type of green algae (Chlorophyta) that contains many important bioactive compounds such as sources of antioxidants, namely flavonoids and phenols, as well as steroids that have the potential as anti-infertility. Sources of antioxidants in the Ulva lactuca algae originating from the Gondol Beach of Bali were observed through laboratory testing through phytochemical screening and soxhlet extraction with 96% ethanol. This study aimed to identify and analyze the bioactive compounds in the algae Ulva lactuca as an antioxidant and anti-infertility effect. The research used experimental laboratory and computational methods. The results showed that the Ulva lactuca through the TLC test contained flavonoid, triterpenoid, and steroid bioactive compounds. Through GC-MS test, it contained a sterol product, namely 29-isofucosterol, with a normalized value of 5.6%. Examination using the bioinformatic method metabolites in Ulva lactuca can bind to proteins as well as antioxidant enzymes and sex steroid hormones in women. Ulva lactuca has the potential as an antioxidant and anti-infertility that works synergistically on the reproductive organs. Thus, it can be used for complementary therapy for disorders of the female reproductive system with fertility problems, which has minimal risks and side effects.
Keywords: *Antioxidant-antiinfertility; Bioactive compounds; Ulva lactuca; TLC and GC-MS.*
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INTRODUCTION

Infertility conditions, especially in women, can be experienced due to environmental conditions, in this case, namely unhealthy lifestyles and eating patterns, such as smoking, elevated consumption of caffeine and alcohol, stress, agonist sports, chronic exposure to environmental pollutants, and other nutritional habits exert a negative impact on a women's fertility,[1] like frequent consumption of foods that contain lots of harmful substances, food additive and instant foods that can interfere with the health of reproductive organs.[2] One of the disturbances in reproductive health is the mechanism of action of sex steroid hormones in the body, which are important for maintaining the reproductive system. Sex steroid hormones are important in women, such as oestrogen and progesterone. Besides that, testosterone is also important in regulating the hormonal system in women.[3] Disturbances in the working mechanism of hormones can be shown in the imbalance of these hormones. Thus, they can impact disorders of the female reproductive system and organs.[4]

Restoration of the reproductive system due to hormonal disorders can be overcome in various ways, either with medication, one of which is drugs or hormone replacement, or non-medical such as therapy with traditional or complementary substances. Complementary therapy is an alternative therapy that uses natural or herbal ingredients as a treatment medium. Currently, it is widely used in the community because it is considered to have minimal side effects or risks and is very affordable.[5,6] The provision of herbal medicine is considered one of the therapies used to restore hormonal disorders that occur in the working mechanism of the reproductive system and cause female infertility.[7] The use of natural ingredients from natural sources can be used as a safe and easily available therapy.[8] One example of natural materials is algae or marine algae found on the Gondol beach in Bali.

Algae is a marine biota consisting of green, red, and brown algae. Green algae, known as *Chlorophyta*, is a type of algae widely distributed in Indonesian waters.[9,10] Green algae also have many specifications according to the characteristics of the plant and where it grows.[11] The green algae species *Ulva lactuca* is a species of green algae that

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is commonly found on the Gondol beach in Bali and is often used as a food source. Green algae are a source of natural ingredients that have major potential in the fields of food, agriculture, and pharmaceuticals[12,13] because they are rich in nutrients such as carbohydrates, protein, vitamin B, vitamin C, vitamin E, amino acids, zinc, iron, fibres, and pigments that contain little lipids.[14,15] In addition to these nutritional sources, green algae are also known to contain bioactive compounds that are useful as antioxidants and anti-inflammatory because there are ingredients such as flavonoids, phenols, tannins, and steroids.[16,17]

In vitro and in vivo on experimental animals proved that the green algae *Ulva lactuca* through HPLC (high-performance liquid chromatography) and gel permeation chromatography methods contain polysaccharides, which can act as protectors for the kidneys and liver, namely by preventing and being able to cause a healing effect on the kidneys and liver.[18] Conditions of nephrotoxicity and hepatotoxicity could be caused by exposure to free radicals or oxidants that cause oxidative stress to cells. Likewise, its effect is neuroprotective for the CNS (Central Nervous System).[19] The next study related to reproduction was that supplementation of seaweed *(Ulva lactuca)* in male and female rabbits resulted in increased seminal fluid in males and proliferative characteristics in females.[20]

The administration of *Ulva lactuca* water fraction to under oxidative stress conditions of cells from male rats improves oxidative stress and downregulates the expression of pro-inflammatory marker genes.[21] This shows that this green alga has the potential as an antioxidant as well as a therapy for male infertility. The body's natural types of antioxidant enzymes that work in known antioxidant regulatory systems are glutathione peroxidase (Gpx), Catalase (CAT), glutathione transferase (GST), and Superoxide dismutase (SOD).[22] The antioxidant system works in the body in various ways, such as breaking down free radicals enzymatically or by direct chemical reactions, breaking down lipid peroxyl radicals, binding to metal ions, and repairing oxidative damage.[23]

Antioxidants function to add or remove one electron to neutralize reactive oxygen species (ROS). Thus, free radicals become stable and inhibit the oxidation process.[24,25] The mechanism of action on a peptide or other molecules such as a neurotransmitter, hormone, drug, or toxin before starting the biological activity in cells is assisted by signalling called signal transduction, beginning with a meeting between the ligand (compound) and the target protein.[26] The protein or known as this receptor, will detect the signal stimulation carried by its specific ligand so that it will produce cellular responses in various forms that can affect the development of these cells. Receptors attached to target cells can be in the membrane, cytoplasm, or nucleus of the cell.[27]

The activity of sex steroid hormones in the reproductive system will involve the participation of receptors and their ligands. Receptors that play a role are androgen receptors, oestrogen receptors, and progesterone receptors, while the ligands are the hormones testosterone, oestrogen, and progesterone, respectively. The binding that occurs between the receptor and the ligand will form a hormone-receptor complex, which then causes processes in the cell, including differentiation and proliferation as the target cell's response to the presence of the hormone.[28] The working system of sex steroid hormones after the binding occurs between the receptor and its ligand on an element in the intracellular area or nucleus. Then there is an activation of transcription and translation factors so that new proteins will be formed that is useful for the survival of the cells of these organs.[29,30]

This study wanted to prove the presence of bioactive compounds in green algae species *Ulva lactuca*, especially those from Gondol beach Bali through thin layer chromatography/TLC and GC-MS tests. In addition, the researchers also want to analyse its use using the bioinformatics method. The use of these two methods aims to determine whether the metabolite compounds in green algae *Ulva lactuca* can be potential as antioxidants to improve the reproductive system in women with disorders, and their role as anti-infertility, especially for women through the content of steroids and sterols in green algae *Ulva lactuca* which have not been widely discussed in previous studies.

MATERIALS AND METHODS

Materials

The tools and materials for phytochemical screening used are mortar, Soxhlet, 96% ethanol solvent, rotary evaporator, oven, TLC plate. Materials for computational are HP brand laptops with Intel processor (R) Core (TM) i5 processor specifications, 4GB of RAM, and Windows 10 OS, 64 bits, Marvin View 6 software. Programs used for molecular docking stages are PyRx, Auto dock Vina, PyMOL, Open babel 2.3.1, and discovery studio client 2021 (Biovia). Discovery studio applications are used to visualize and analyze docking results between ligands prepared from compounds contained in marine algae, and proteins used as targets are specific proteins in the ovaries. Databases used to prepare target compounds and proteins, namely UniProt, Swiss Target Prediction, PASS Online, PubChem, protein data bank/PDB.

Methods

The research method used in this study was an experimental laboratory method by observing and detecting the content contained in the green algae *Ulva lactuca* taken from Gondol beach Bali using a phytochemical screening method with TLC test and GC-MS. After that, it was continued by analyzing through computational bioinformatic methods to determine the

biological effects of metabolite compounds, especially on hormonal regulation in the reproductive system, which is associated with fertility, as well as the potential for organ recovery if it is associated with its antioxidant effects.

RESULTS AND DISCUSSION

Results

Table 1. TLC test results of green algae ethanol extract *Ulva lactuca*

No	Metabolites	TLC test technique	Reagent	Result	Category
1	Flavonoid	Stationary phase = Kiesel gel thin layer GF 254 Mobile phase= Butanol: glacial acetic acid: water (4:1:5)	ammonia vapor, UV 366 nm and 254 nm	yellow stain	(+)
2	Polifenol	Stationary phase: Kiesel Gel thin layer GF 254 Mobile phase: ethyl acetate: methanol: formic acid (16:4:1)	FeCl3 2 %, UV 3 nm and 254 nm	Ferrichloride test: A dark blue-green stain appears TLC test: no black spots appear	(-)
3	Terpenoid	Stationary phase = kiesel gel GF 254 Mobile phase= n hexane: ethyl acetate (4:1)	Sulfuric acid anisaldehyde	Purple	(+)
4	Steroid	Stationary phase = kiesel gel GF 254 Mobile phase= n hexane: ethyl acetate (4:1)	Sulfuric acid anisaldehyde	Purple	(+)

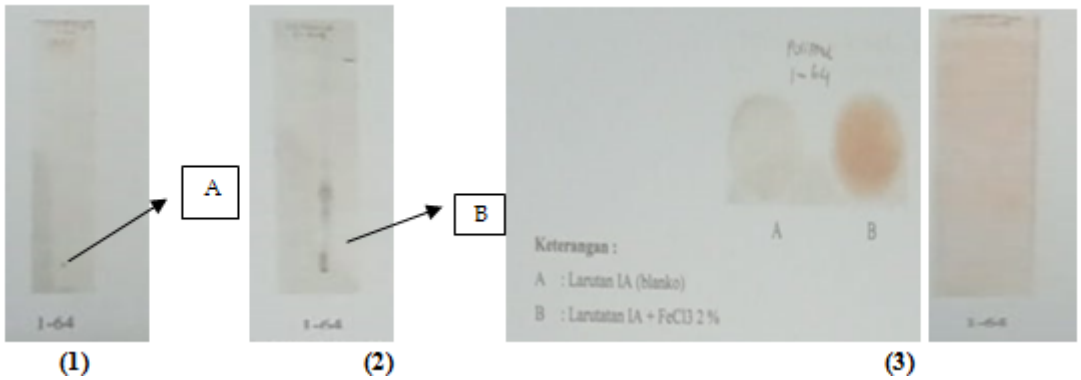

Figure. 1 Phytochemical screening results

(1). Flavonoid screening, A. yellow stain, (2). Steroid screening, B. purple stain, (3). Polyphenol screening (left - Ferricchloride test, right - TLC test)

Table. 2 GC-MS test results on green algae compounds *Ulva lactuca*

No	Compound name	% Normalization	Qual
1	Cyclopentane	0,39	91
2	Phenol, 2-methoxy-5-(2-propenyl)	0,60	98
3	8-Heptadecane	0,26	99
4	Myristic acid	0,63	99
5	Neophytadiene	2,17	99
6	Hexadecenoic acid	1,57	98
7	Palmitic acid	13,26	99
8	Octadec-9-enoic acid	4,64	99
9	Stearate	0,47	99

No	Compound name	% Normalization	Qual
10	Cyclotriidecane	0,76	95
11	Abreva	0,93	93
12	29-Isofucosterol	5,83	94

Table. 3 Prediction of target ligands and biological activity of compounds

No	Ligand	Formula	Protein	Activity	pa
1	Cyclopentane	C5H10	Nuclear receptor	CYP2J substrate, Mucomembranous protector, GST A substrate	0,901; 0,833; 0,774
2	Phenol, 2-methoxy-5-(2-propenyl)	C6H5OH	AR, ERα, ERβ, PR, steroidαR	CYP2E1 substrate, Apoptosis, CYP2C12 substrate	0,856; 0,743; 0,734
3	8-Heptadecane	C17H3	AR, ERα	CYP2J substrate, GST A substrate, CYP2C12 substrate	0,948; 0,904; 0,894
4	Myristic acid	C14H28O	PR	CYP2J substrate, GST A substrate, CYP2C12 substrate, CYP4A11 substrate	0,962; 0,902; 0,877; 0,825
5	Neophytadiene	C20H38	AR, PR, VDR, GSTR	CYP2J substrate	0,720
6	Hexadecenoic acid	C16H32O2	AR, PR, VDR, GSTR	CYP2J substrate, CYP2C12 substrate, lipid metabolism regulator, anti-inflammatory	0,962; 0,877; 0,808; 0,727
7	Palmitic acid	C16H3O2	AR, PR, ERα, ERβ, VDR, GSTR, steroidαR, SREBPR	CYP2J substrate, GST A substrate, CYP2C12 substrate, GST P1-1 substrate, CYP2C9 substrate	0,961; 0,902; 0,877; 0,834; 0,802
8	Octadec-9-enoic acid	C18H34O2	AR, PR, ERα, ERβ, VDR, GSTR	CYP2J substrate, CYP4A2 substrate, CYP3A1 substrate, CYP2C12 substrate, UGT2B1 substrate	0,974; 0,869; 0,805; 0,804; 0,721
9	Stearate	C18H35O2	Nuclear receptor	CYP2J substrate, GST A substrate, CYP2J2 substrate, CYP2C12 substrate, Peptide agonist, Antiinfective	0,935; 0,876; 0,855; 0,850; 0,827; 0,764
10	Cyclotriidecane	C13H26	AR, PR, ERα, ERβ, VDR, GSTR, SREBPR	CYP2C12 substrate, CYP2J2 substrate, Vasoprotector, Vasoprotector, GST A substrate	0,896; 0,860; 0,783; 0,774
11	Abreva	C22H46O	AR, PR, VDR, GSTR	CYP2C12 substrate; CYP2J2 substrate; GST A substrate	0,908; 0,881; 0,876
12	29-Isofucosterol	C29H48O	AR, PR, ERα, ERβ	UGT1A substrate, UGT2B substrate, CYP2J2 substrate, CYP2C11 substrate, UGT2B1 substrate, CYPC19 substrate, Antiinfertility female	0,902; 0,856; 0,780; 0,753; 0,726; 0,720; 0,702

Source: Primary data processed in 2022

Table. 4 Target proteins and binding site

No	Protein	PDB ID	RSMD	Binding site/control
1	Androgen receptor (AR)	2q7i	1,87Å	TES-Testosterone ($C_{19}H_{28}O_2$)
2	Estrogen receptor alpha (ERα)	1r5k	2,70 Å	E2-Estradiol ($C_{18}H_{24}O_2$)

				GW5638 ($C_{25}H_{22}O_2$)
3	Estrogen receptor beta (ERβ)	1u3q	2,40 Å	E2-Estradiol (C18H24O2) CL-272 ($C_{13}H_9NO_4$)
4	Progesteron receptor (PR)	1a28	1,80Å	STR-Progesterone ($C_{21}H_3O_2$)
5	Vitamin D receptor (Vit DR)	5xzf	2.10 Å	8JO (C_{35} H_{50} O_3) FMT (C H_2 O_2)
6	Steroid alpha receptor (SteroidαR)	7bw1	2.80 Å	NDX (C_{44} H_{66} N_9 O_{19} P_3) OLC (C_{21} H_{40} O_4) S04 (O_4 S)
7	Sterol regulatory element binding receptor (SREBPR)	4uhl	2.50 Å	HEM (C_{34} H_{32} Fe N_4 O_4) VFV (C_{32} H_{23} F_2 N_5 O_2)
8	Glutathione receptor (GSTR)	3rpn	1.90 Å	GTX (C_{16} H_{30} N_3 O_6 S)

Source: Primary data processed in 2022

Table 5. Results of molecular docking of the ligand complex with the target protein

No	Compounds	Binding affinity								
		Target protein/ receptor								
		AR	ER	ERa	ERb	PR	VDR	Steroid αR	(SRE BPR)	GSTR
1	Control	-6.60	-10.90	-7.10, -7.40	-10.60, -6.80	-8.10	-2.80	-6.60	-12.40	-6.50
2	Cyclopentane	-4.20	-3.70	-3.80	-3.60	-3.90	-4.10	-3.80	-4.00	-3.50
3	Phenol, 2-methoxy-5-(2-propenyl)	-6.20	-5.90	-4.90	-6.50	-5.90	-6.80	-6.00	-5.80	-5.60
4	8-Heptadecane	-5.60	-5.40	-5.20	-4.00	-4.70	-6.70	-5.90	-5.30	-5.60
5	Myristic acid	-4.40	-5.30	-4.80	-6.40	-5.70	-7.00	-6.00	-5.60	-5.70
6	Neophytadiene	-4.60	-5.90	-4.10	-7.00	-5.50	-7.20	-6.70	-5.80	-6.50
7	Hexadecenoic acid	-4.90	-4.60	-3.90	-6.90	-5.80	-7.20	-6.20	-5.70	-5.80
8	Palmitic acid	-4.60	-5.00	-5.20	-3.80	-5.20	-7.40	-6.20	-5.10	-7.50
9	Octadec-9-enoic acid	-5.30	-5.00	-4.50	-7.20	-5.80	-6.50	-6.70	-5.60	-6.10
10	Stearate	-6.20	-4.90	-4.60	-6.90	-4.90	-7.20	-6.30	-5.40	-6.10
11	Cyclotriidecane	-5.20	-7.70	-5.00	-8.00	-6.80	-7.20	-7.10	-6.50	-6.90
12	Abreva	-4.60	-4.60	-4.40	-3.90	-4.90	-6.60	-6.20	-5.00	-5.90
13	29-Isofucosterol	-7.50	-7.60	-6.90	-6.20	-8.70	-11.80	-11.80	-9.80	-8.50

Source: Primary data processed in 2022

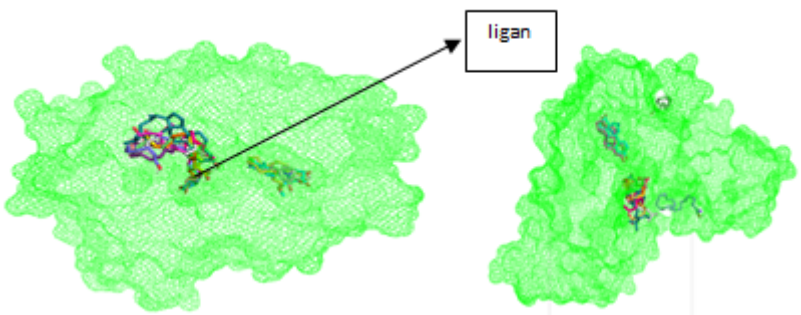

Figure 2. The docking results of the ligand and receptor complex (AR_left), (ER_right)

Table 6. Analysis of docking results (binding of ligand compounds to receptors)

Protein	Compound/ ligand	Interaction amino acid	Distance (Å)	Compound/ ligand
AR	Control	1. TRP751	2,93	Hydrogen bond
		2. ARG752	3,24	Hydrogen bond
		3. GLY683	3,34	Electrostatic
		4. GLU681	3,84	Electrostatic
		5. PRO801	5,2	Hydrophobic
	Cyclopentane	1. PRO682	4,86	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1. ASN705	3,07	Hydrogen bond
		2. THR877	3,24	Hydrogen bond
	8-Heptadecane	1. PRO682	4,03	Hydrophobic
		2. ARG752	4,89	Hydrophobic
		3. TRP751	5,13	Hydrophobic
	Myristic acid	1. GLN711	3,28	Hydrogen bond
		2. ARG751	2,93	Hydrogen bond
		3. PRO801	5,06	Hydrophobic
		4. TRP751	5,15	Hydrophobic
	Neophytadiene	1. ARG752	5,09	Hydrophobic
		2. PRO801	4,55	Hydrophobic
		3. TRP751	4,69	Hydrophobic
	Hexadecenoic acid	1. LYS808	3,20	Hydrogen bond
		2. PRO682	4,64	Hydrogen bond
		3. ARG752	4,31	Hydrophobic
		4. TRP751	4,95	Hydrophobic
	Palmitic acid	1. GLN711	3,17	Hydrogen bond
		2. ARG752	4,36	Hydrophobic
		3. TRP751	5,04	Hydrophobic
	Octadec-9-enoic acid	1. PRO682	3,71	Hydrophobic
		2. ARG752	4,44	Hydrophobic
		3. TRP751	5,29	Hydrophobic
	Stearate	1. ASN705	3,13	Hydrogen bond
		2. THR877	3,00	Hydrogen bond
	Cyclotriidecane	-	-	-
	Abreva	1. PRO682	4,54	Hydrophobic
		2. ARG752	5,03	Hydrophobic
		3. TRP751	4,49	Hydrophobic
		4. PRO801	5,48	Hydrophobic
	29-Isofucosterol	1. VAL685	3,10	Hydrogen bond
		2. ARG752	4,48	Hydrophobic
		3. TRP751	4,95	Hydrophobic
ER	Control	1. HIS524	3,07	Hydrogen bond
		2. EST596	2,49	Hydrogen bond
		3. MET388	4,72	Hydrophobic
		4. PHE404	5,39	Hydrophobic
	Cyclopentane	1. ALA350	4,41	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1. ARG394	2,80	Hydrogen bond
	8-Heptadecane	1. ARG394	4,79	Hydrophobic
		2. PHE445	5,42	Hydrophobic
	Myristic acid	1. MET357	3,11	Hydrogen bond
		2. ARG394	4,67	Hydrophobic
	Neophytadiene	1. PRO324	5,22	Hydrophobic
	Hexadecenoic acid	1. PRO324	5,31	Hydrophobic

		2.	ARG394	4,33	Hydrophobic
	Palmitic acid	1.	SER537	3,25	Hydrogen bond
		2.	PRO535	2,22	Hydrogen bond
	Octadec-9-enoic acid	1.	PRO324	5,26	Hydrophobic
		2.	ARG394	4,84	Hydrophobic
		3.	MET357	3,89	Hydrophobic
	Stearate	1.	PRO324	5,07	Hydrophobic
		2.	ARG394	4,17	Hydrophobic
	Cyclotriidecane	1.	LEU384	4,74	Hydrophobic
	Abreva	1.	ASN42	3,07	Hydrogen bond
		2.	HIS356	5,05	Hydrophobic
	29-Isofucosterol	1.	PRO324	3,99	Hydrophobic
		2.	ARG394	4,92	Hydrophobic
ERα	Control	1.	LYS449	3,00	Hydrogen bond
		2.	ARG394	5,26	Electrostatic
		3.	ILE326	3,49	Hydrophobic
		4.	ALA493	3,80	Hydrophobic
		5.	EST596	4,22	Hydrophobic
		6.	GW5600	4,99	Hydrophobic
	Cyclopentane	1.	ALA350	3,84	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1.	ARG515	3,65	Hydrogen bond
		2.	ILE451	4,77	Hydrophobic
	8-Heptadecane	1.	PRO324	4,98	Hydrophobic
	Myristic acid	1.	ARG503	3,10	Hydrogen bond
		2.	ALA493	4,10	Hydrophobic
	Neophytadiene	1.	ALA430	3,77	Hydrophobic
		2.	ARG434	4,53	Hydrophobic
	Hexadecenoic acid	1.	ARG434	2,86	Hydrogen bond
		2.	ALA430	4,19	Hydrophobic
	Palmitic acid	1.	PRO324	4,74	Hydrophobic
		2.	ILE326	4,69	Hydrophobic
	Octadec-9-enoic acid	1.	PRO324	5,25	Hydrophobic
		2.	ARG394	5,33	Hydrophobic
		3.	ILE326	5,08	Hydrophobic
	Stearate	1.	LYS449	3,15	Hydrogen bond
		2.	PRO324	5,34	Hydrophobic
		3.	ARG394	4,43	Hydrophobic
		4.	ILE326	5,31	Hydrophobic
	Cyclotriidecane	-			
	Abreva	1.	PRO324	5,04	Hydrophobic
		2.	ARG394	4,83	Hydrophobic
	29-Isofucosterol	1.	ARG515	4,78	Hydrophobic
ERβ	Control	1.	PHE356	4,93	Hydrophobic
		2.	LEU298	5,32	Hydrophobic
		3.	MET340	5,19	Hydrophobic
		4.	HIS475	4,70	Hydrophobic
		5.	EST596	4,50	Hydrophobic
	Cyclopentane	1.	LEU343	4,95	Hydrophobic
		2.	PHE356	5,39	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1.	HIS279	3,23	Hydrogen bond
	8-Heptadecane	1.	MET494	5,45	Hydrophobic
		2.	PHE325	4,64	Hydrophobic
	Myristic acid	1.	PHE356	5,19	Hydrophobic

	Neophytadiene	1.	MET340	4,05	Hydrophobic
		2.	PHE356	5,25	Hydrophobic
		3.	HIS475	4,81	Hydrophobic
	Hexadecenoic acid	1.	MET340	5,40	Hydrophobic
		2.	PHE356	4,92	Hydrophobic
		3.	HIS475	4,94	Hydrophobic
	Palmitic acid	1.	TYR488	3,15	Hydrogen bond
	Octadec-9-enoic acid	1.	HIS475	3,03	Hydrogen bond
		2.	MET340	4,00	Hydrophobic
		3.	LEU298	4,64	Hydrophobic
		4.	PHE356	5,09	Hydrophobic
	Stearate	1.	HIS475	2,89	Hydrogen bond
		2.	LEU298	4,52	Hydrophobic
		3.	MET340	3,98	Hydrophobic
		4.	PHE356	5,03	Hydrophobic
	Cyclotriidecane	1.	LEU298	4,74	Hydrophobic
	Abreva	1.	MET296	4,72	Hydrophobic
	29-Isofucosterol	1.	LEU298	4,92	Hydrophobic
PR	Control	1.	PHE905	3,21	Hydrophobic
		2.	PHE895	4,70	Hydrophobic
	Cyclopentane	1.	ILE804	4,83	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1.	THR829	2,84	Hydrogen bond
	8-Heptadecane	1.	PHE895	4,16	Hydrophobic
	Myristic acid	1.	PHE905	3,37	Hydrogen bond
	Neophytadiene	1.	PHE895	4,13	Hydrophobic
	Hexadecenoic acid	1.	PHE905	2,88	Hydrogen bond
		2.	PHE895	3,80	Hydrophobic
	Palmitic acid	1.	PHE905	3,22	Hydrogen bond
		2.	PHE895	4,00	Hydrophobic
	Octadec-9-enoic acid	1.	PHE905	3,05	Hydrogen bond
		2.	PHE895	4,30	Hydrophobic
	Stearate	1.	PHE895	4,29	Hydrophobic
	Cyclotriidecane	1.	LEU718	5,02	Hydrophobic
	Abreva	1.	PHE905	3,63	Hydrogen bond
		2.	PHE895	3,80	Hydrophobic
	29-Isofucosterol	1.	PHE905	2,31	Hydrogen bond
		2.	PHE895	4,04	Hydrophobic
VDR	Control	1.	ARG339	2,85	Hydrogen bond
		2.	ARG387	3,02	Hydrogen bond
	Cyclopentane	1.	TRP282	4,17	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1.	TRP282	4,00	Hydrophobic
	8-Heptadecane	1.	TRP282	4,13	Hydrophobic
	Myristic acid	1.	ARG270	2,92	Hydrogen bond
		2.	TRP282	4,08	Hydrophobic
	Neophytadiene	1.	TRP282	4,51	Hydrophobic
	Hexadecenoic acid	1.	ARG270	2,90	Hydrogen bond
		2.	TRP282	3,66	Hydrophobic
	Palmitic acid	1.	TRP282	3,67	Hydrophobic
	Octadec-9-enoic acid	1.	ARG270	3,20	Hydrogen bond
		2.	TRP282	4,53	Hydrophobic
	Stearate	1.	TRP282	4,32	Hydrophobic

SRBPR	Cyclotriidecane	1.	TRP282	5,44	Hydrophobic
	Abreva	1.	TRP282	3,66	Hydrophobic
	29-Isofucosterol	1.	TRP282	3,88	Hydrophobic
	Control	1.	HIS314	3,93	Hydrophobic
		2.	PHE139	5,33	Hydrophobic
		3.	PHE152	5,26	Hydrophobic
	Cyclopentane	1.	PHE105	3,77	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1.	PHE442	4,84	Hydrophobic
	8-Heptadecane	1.	PHE152	4,92	Hydrophobic
		2.	PHE139	4,01	Hydrophobic
	Myristic acid	1.	PHE152	4,69	Hydrophobic
	Neophytadiene	1.	PHE139	4,34	Hydrophobic
		2.	PHE152	5,19	Hydrophobic
	Hexadecenoic acid	1.	PHE139	4,11	Hydrophobic
	Palmitic acid	1.	PHE139	5,07	Hydrophobic
		2.	PHE152	4,79	Hydrophobic
	Octadec-9-enoic acid	1.	HIS447	3,16	Hydrogen bond
		2.	PHE139	4,16	Hydrophobic
		3.	PHE152	5,22	Hydrophobic
	Stearate	1.	PHE139	4,14	Hydrophobic
		2.	PHE152	5,49	Hydrophobic
	Cyclotriidecane	1.	PHE234	3,72	Hydrophobic
	Abreva	1.	PHE234	3,81	Hydrophobic
		2.	HIS314	4,90	Hydrophobic
	29-Isofucosterol	1.	HIS314	3,41	Hydrogen bond
		2.	PHE234	3,57	Hydrophobic
		3.	PHE105	5,22	Hydrophobic
SteroidαR	Control	1.	ARG94	2,93	Hydrogen bond
		2.	TRP53	4,65	Hydrophobic
		3.	PHE118	5,35	Hydrophobic
		4.	PHE216	5,07	Hydrophobic
		5.	PHE219	5,24	Hydrophobic
		6.	PHE223	4,53	Hydrophobic
	Cyclopentane	1.	PHE118	4,65	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1.	PHE223	5,00	Hydrophobic
	8-Heptadecane	1.	TRP53	5,45	Hydrophobic
		2.	PHE118	4,23	Hydrophobic
		3.	PHE216	5,09	Hydrophobic
		4.	PHE219	5,36	Hydrophobic
		5.	PHE223	4,33	Hydrophobic
	Myristic acid	1.	PHE118	4,41	Hydrophobic
		2.	PHE216	4,95	Hydrophobic
		3.	PHE219	5,27	Hydrophobic
		4.	PHE223	4,36	Hydrophobic
	Neophytadiene	1.	PHE118	4,42	Hydrophobic
		2.	TRP53	4,49	Hydrophobic
		3.	PHE219	5,18	Hydrophobic
		4.	PHE223	4,82	Hydrophobic
	Hexadecenoic acid	1.	ARG94	2,97	Hydrogen bond
		2.	TRP53	5,13	Hydrophobic
		3.	PHE118	4,41	Hydrophobic
		4.	PHE223	4,51	Hydrophobic

	Palmitic acid	1.	TRP53	4,55	Hydrophobic
		2.	PHE118	4,62	Hydrophobic
		3.	PHE219	4,67	Hydrophobic
		4.	PHE223	4,16	Hydrophobic
	Octadec-9-enoic acid	1.	ARG94	2,95	Hydrogen bond
		2.	TRP53	4,63	Hydrophobic
		3.	PHE118	4,55	Hydrophobic
		4.	PHE223	4,37	Hydrophobic
	Stearate	1.	TRP53	4,99	Hydrophobic
		2.	PHE118	4,45	Hydrophobic
		3.	PHE223	4,67	Hydrophobic
	Cyclotriidecane	1.	PHE118	3,84	Hydrophobic
		2.	PHE223	5,18	Hydrophobic
	Abreva	1.	TRP53	5,31	Hydrophobic
		2.	PHE118	4,04	Hydrophobic
		3.	PHE216	5,31	Hydrophobic
		4.	PHE219	5,28	Hydrophobic
		5.	PHE223	4,75	Hydrophobic
	29-Isofucosterol	1.	TRP53	4,77	Hydrophobic
		2.	PHE118	5,43	Hydrophobic
		3.	PHE223	4,47	Hydrophobic
GSTR	Control	1.	LYS62	5,38	Hydrophobic
		2.	PRO56	3,57	Hydrogen bond
		3.	GTX302	4,19	Hydrophobic
	Cyclopentane	1.	PRO55	5,34	Hydrophobic
	Phenol, 2-methoxy-5-(2-propenyl)	1.	PRO55	5,45	Hydrophobic
	8-Heptadecane	1.	PRO56	4,99	Hydrophobic
		2.	PRO55	5,42	Hydrophobic
	Myristic acid	1.	PRO56	3,54	Hydrogen bond
		2.	PRO55	4,73	Hydrophobic
	Neophytadiene	1.	PRO56	4,77	Hydrophobic
		2.	PRO55	4,80	Hydrophobic
	Hexadecenoic acid	1.	PRO56	4,40	Hydrophobic
	Palmitic acid	1.	PRO56	4,24	Hydrophobic
		2.	PRO55	5,22	Hydrophobic
	Octadec-9-enoic acid	1.	PRO55	5,28	Hydrophobic
		2.	PRO56	4,15	Hydrophobic
	Stearate	1.	PRO56	4,80	Hydrophobic
	Cyclotriidecane	1.	PRO56	5,34	Hydrophobic
	Abreva	1.	PRO55	4,82	Hydrophobic
		2.	PRO56	4,48	Hydrophobic
	29-Isofucosterol	1.	PRO56	4,61	Hydrophobic
		2.	LYS62	3,94	Hydrophobic

Source: primary data processed in 2022

DISCUSSION

Based on research (table 1 and 2) that has been carried out experimental in the laboratory by carrying out phytochemical screening using the TLC method, followed by testing the compounds contained in the *Ulva lactuca* algae extract using the GC-MS test, and based on the results of a qualitative examination with phytochemical screening, namely TLC, it is known that the green algae *Ulva lactuca* found at Gondol beach Bali contain secondary metabolites such as flavonoids and triterpenoids as well as steroids. However, when testing the polyphenol group, no color deposits indicated these compounds' presence. In contrast, the GC-MS test found the presence of phenolic compounds with a normalized area percentage of 0.60%. Table. 2 shows that several compounds are contained in the green algae extract *Ulva lactuca*, qualitatively indicated by the percentage of the normalized area and the qualitative value of the compound content

above 90. The percentage of the normalized area cannot show the exact number of compound compositions contained in the extract.

The results of the GC-MS test show the content of several compounds and the percentage of normalization of the content area in the green algae extract *Ulva lactuca*. This normalized percentage value does not show a quantitative value or the actual number of compound compositions because this test is qualitative. Thus, if the qualitative value is less than 90, the compound's identity in the material is undetected. Thus, there are still many compounds in the *Ulva lactuca* algae that are unknown because they have a low qualitative value. The palmitic acid compound is a compound that has the largest percentage of normalized area, namely 13.26%, which indicates that this compound is detected at the largest on the surface area of the *Ulva lactuca* algae because it has a higher standard value than other compounds, with a standard qualitative value of 99. Palmitic acid compounds are one of the saturated long-chain fatty acids easily obtained from plants,[31] containing Hexadecanoic in the database test results with KEGG (Kyoto encyclopedia of genes and genomes) compounds.

Table 3 shows that the target protein is a receptor both in the intracellular and cell membrane. The level of accuracy of the biological activity of the compound was tested with PASS online and expressed by the value of potential activity/pa.[32,33] Based on the predicted results of biological activity in compounds traced from the online pass database, it shows that Palmitic acid compounds have activity as a substrate for the glutathione enzyme (GST), with a pa (potential activity) value of 0.902> pa 0.7 which means it has very high biological activity. The results were not significantly different from the laboratory test. If the pa value is more than 0.5 but less than 0.7 ($0.5 < pa < 0.7$), then the compound has a high enough biological activity and becomes a bioactive compound in vitro and or in vivo experimental tests and, at the same time, has the potential for the development of drug compounds.[32,34] GST enzyme is one of the body's endogenous antioxidants that protects cells from toxic effects and free radicals.[31] Therefore, Palmitic acid is a compound that can act as a natural antioxidant.

In the KEGG reaction test, it was found that phenol compounds play a role in a reaction, namely oxidoreductase. Oxidoreductases are enzymes that catalyze the transfer of electrons from one molecule (reductant/electron donor) to another molecule or oxidant (electron acceptor).[35] Thus, the number of unpaired electron atoms under conditions of oxidative stress becomes paired and stable due to electron donors by antioxidant sources. Phenolic compounds are the largest group of compounds that act as natural antioxidants in plants.[36] Predicting the biological activity of phenol plays a role in apoptotic events, which are also important for cell survival. This shows that the role of phenolic compounds is the same as that of flavonoids, namely as a source of natural antioxidants originating from outside the body or exogenous. Several other compounds were also found to be contained in the algae *Ulva lactuca* and have been predicted to be antioxidants based on the activity of compounds that act as GST substrates, *Cyclopentane, Heptadecane, Myristic acid, Stereate, Cyclotriidecane, and Abreva*.

The next compound found in the *Ulva lactuca* algae extract was 29-isofucosterol, with a normalized percentage value of 5.83% with a qualitative value of 94. This compound is a sterol group compound, also known as steroid alcohol, a subgroup of steroids and an important group of organic molecules. Sterols occur naturally in plants, animals, and fungi, in the most well-known form, cholesterol. Cholesterol is an important component of the structure of animal cell membranes and serves as a precursor for fat-soluble vitamins and steroid hormones.[37,38] This condition is also in line with the results of the TLC screening, which showed that the green algae *Ulva lactuca* contained terpenoid/free steroid compounds which were viewed qualitatively. The compound 29-isofucosterol has biological activity as a substrate for UGT1A with a pa value of 0.902 (> pa 0.7), indicating a very high accuracy value. The enzyme UGT1A (UDP Glucuronosyltransferase Family 1 Member A1) is an enzyme that plays a role in the regulation of sex steroid hormones in the regulation of the reproductive system. Likewise, the biological activity found in the compound 8-Heptadecane, namely as a substrate for CYP2C12 (cytochrome P450 family two subfamily C member 12), this enzyme also plays a role in the reproductive system.

The target proteins found in the compounds contained in the *Ulva lactuca* algae are nuclear/intracellular receptors such as AR, ERα, ERβ, PR, VDR, steroidαR, SREBPR, and extracellular receptors such as GSTR.[39,40] Through the therapeutic target database on the page http://db.idrblab.net/ttd/, the target protein in female infertility is the oestrogen receptor. Thus, ER is also used as a target protein. Before this target protein is used in the docking process as a receptor, a quality test is carried out first by looking at the RSMD (Ramachandran) value through the PDB database (protein data bank). If the RSMD is between 1-3 and has a minimum value of 90%, the protein quality is very good and can be used as a target protein for the docking process.[41] Afterwards, the target protein/receptor will be paired with a compound in the *Ulva lactuca* algae that acts as a ligand to determine the interactions or bonds that occur between the receptor and the ligand and then compared with the control. Compounds that play a role in control are obtained through the interaction between the receptor and the original ligand.

Table 5 shows the results of the molecular docking process between the ligand and the receptor to form strong bonds and interactions expressed by the value of binding affinity. The results of the molecular docking process of compounds with predetermined receptors are shown by the value of the binding affinity. The lower the affinity value obtained in the docking process, the less energy released by a compound to interact or form a bond with the receptor is small, and vice versa.[42] Thus, the bond or interaction becomes stronger because energy that comes out during the bonding process is very low. The binding affinity values for 29-isofucosterol compounds with target proteins such as AR, ER, PR, VDR, steroidαR, SREBPR, and GSTR have affinity values of -7.50, -7.60, -8.70, -11.80, -11.80, -9.80 and -8.50, respectively. This shows that the 29-isofucosterol compound has a fairly strong bond compared to the above receptor, while the receptor's binding to the control has values of -6.60, -10.90, -8.10, -2.80, -6.60, -12.40, -6.50 respectively. Based on this, it shows that the binding affinity value between the isofucosterol compound and each receptor is better than the interaction of the compound with the control, except for the binding affinity value in the control oestrogen, which shows a lower value than the 29-isofucosterol compound.

The control binding affinity value with AR is known to be greater than that of isofucosterol compounds. Likewise, for VDR and GSTR, which are known to play a role in cell repair due to damage by free radicals, or play a role in the antioxidant system, it can be seen that their affinity values are lower than controls. This shows that this compound can bind to target proteins for the reproductive system, such as sex steroid hormone receptors. At the same time, it can bind well with target proteins/receptors in the antioxidant system. Palmitic acid, also strongly suspected of being an antioxidant, has an affinity for binding with VDR and GSTR, which are -7.40 and -7.50, respectively, smaller than the binding affinity for the receptor with the control. This condition indicates that the Palmitic acid compound is suitable for the receptor because it has a strong bond that can be used as a source of natural antioxidants.

The results of molecular docking visualization in this study show several types of interactions that occur in the molecular docking process between the ligand and the target protein, namely hydrogen chain bonds, hydrophobic interactions, and electrostatic interactions. Hydrogen chain bonds are the best bonds compared to other types of bonds. Hydrogen bonding involves the interaction of covalently bonded hydrogen atoms with electronegative atoms such as flour (F), nitrogen (N), and oxygen (O).[43] The similarity of interactions in several amino acids indicates that the compound can interact with the receptor and can cause biological reactions that follow the activity of the receptor along with its control ligands while in the body.

The interaction between AR protein and control ligand (testosterone) on several amino acids, namely the amino acid Tryptophan at number 751 and Arginine at number 752, with the type of interaction being hydrogen chain bonds with a bond distance of 2.93 and 3.24 Angstroms, respectively. These interactions are the same as those that occur in metabolites that act as comparative ligands, namely *Palmitic acid, Myristic acid, Hexadecanoid acid*, and isofucosterol compounds but by forming hydrophobic bonds, which indicates that the compound can act as a ligand as well as a control ligand (testosterone) against AR, and cause reactions that can affect biochemical processes in cells. Hydrophobic interactions also play a role in determining the stability of the ligand to the androgen receptor. Hydrophobic interactions avoid a liquid environment and tend to group inside the protein structure. Electrostatic interactions are interactions between atoms due to differences in their polarity. These interactions include weak and non-covalent interactions so that they are easily separated. Still, because of the large number of electrostatic interactions, they have a major contribution to the formation of protein conformations.[43]

Table 6 shows the analysis results after the molecular docking process between the ligand and the receptor that acts as the target protein. The interactions that occur can be analyzed through the several amino acids involved and the distance between the amino acids, and the bonds formed in these interactions. The study results show that the ligands phenol 2-methoxy-5-(2-propenyl) and Stearate interact with AR on the amino acid THR number 877 with a hydrogen chain bond type with a bond distance of 3.24 Å and 3.00 Å, respectively. But this interaction did not occur in control. This is in line with previous literature showing that hydrogen bonds in the original ligand, namely androgens to androgen receptors, occur in the amino acid ARG number 752, ASN number 702, and THR number 877.[44] Thus, the interaction between AR and control ligands is the same as the interaction of AR with the comparison ligand in the amino acid ARG number 752. Arginine is known to have high hydrophilic properties, which plays an important role in determining a good level of stability in the interaction between the ligand and its receptor. The amino acid is predicted to play an important role in the binding site area in androgen receptors.[43]

Protein binding sites are areas of protein binding to molecules and ions (ligands) that will affect the conformation and function of the target protein. The binding site region involves amino acids that play an important role in binding to the ligand. The interactions between ligands and macromolecular amino acids will form amino acid bonds.[45] The *Myristic acid* ligands, *Neophytadiene*, and *Abreva*, interact with AR at amino

acid PRO number 801, which is the same as the control, with hydrophobic bond types and bond distances of 5.06 Å, 4.55 Å, and 5.48 Å respectively.

The interactions that occur between ER proteins and comparison ligands such as *8-Heptadecane, Octadec-9-enoic acid,* and *Myristic acid* occur in the same amino acids as the interactions between ER and control (oestrogens), namely in the amino acids MET number 388 and PHE number 404 by forming a hydrophobic bond with a bond distance of 5.42 Å and 3.89 Å. The Myristic acid, it forms hydrogen bonds with a distance of 3.11 Å, even closer than in the control. This indicates that the interaction is very good, so the ligand and the target protein can form a strong bond. In ERα protein, interactions that occur with comparison ligands such as *Myristic acid, Palmitic acid, Octadec-9-enoic acid, Stearate,* and *Abreva* compounds have the same amino acid interactions as controls such as LYS number 449, ARG number 394, ILE number 326 and ALA number 493 with varying bond distances. Likewise, the proteins ERβ, PR, steroidαR, and GSTR interact with ligands on some of the same amino acids with ERβ interactions with their controls, with different types of bonds and distances (Table 6). The metabolite compound 29-isofucosterol, known to be a product of sterols and compounds of this steroid group, is not only able to interact well with receptors of steroid hormones and sterols but also with GST receptors. This condition was shown by the similarity of the amino acids PRO number 56 and LYS number 62 with the control so that the 29-isofucosterol compound can function as a steroid ligand and an antioxidant ligand. This proves the role of these metabolites in regulating sex steroid hormones for female fertility and the antioxidant system and is in line with those found in the database, showing that the compound 29-isofucosterol has anti-infertility activity in women.

Based on the results of the docking analysis, it is known that several compounds can interact well with the GSTR. The interactions between GSTR and control ligand (GTX) are amino acids PRO number 56 and LYS number 62, which form hydrophobic bonds and hydrogen chains. Some compounds interacting with the same amino acids are *8-Heptadecane, Myristic acid, Neophytadiene, Hexadecenoic acid, Palmitic acid, Octadec-9-enoic acid, Stearate, Cyclotriidecane, Abreva* and 29-isofucosterol. The results of this study indicate that most of the metabolite compounds contained in the extract of green algae *(Ulva lactuca)* are capable and can interact with target proteins that are known to play a role in the reproductive system, such as 29-isofucosterol compounds, which can interact with GST proteins and also cell nuclear proteins from the ovaries. This shows that this compound can cause antioxidant and anti-infertility effects for women who have experienced hormonal regulation disorders in the reproductive system in the ovaries. Therefore, by consuming this algae plant *(Ulva lactuca)* and using it as herbal therapy, it can improve the condition of cell damage or oxidative stress in body organs including female reproductive organs such as ovaries due to ROS exposure.

CONCLUSION

The results of the study showed that the metabolite compounds in the green algae *Ulva lactuca* species on Gondol beach Bali were antioxidants and steroids, and both were able to interact or bind well with target proteins or body antioxidant receptors and sex steroid hormone receptors found in the ovaries. Therefore, the content of metabolites in green algae *Ulva lactuca* can act as a natural antioxidant as well as anti-infertility, which is thought to work synergistically in the female reproductive organs in the recovery of a disturbed reproductive system. Still, under normal conditions, the effect of this extract can act otherwise. Thus, the advantages of *Ulva lactuca* algae besides is containing steroids or sterols that play a role in hormonal regulation in the reproductive system, it also has several types of antioxidants such as flavonoids and phenols that are able to neutralize by adding hydrogen electron atoms to free radicals/reactive oxygen species thus, that they can contribute to the restoration of reproductive organs. women in addition to the role of sterols. This is considered better than the direct administration of exogenous hormones which are riskier and have side effects.

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Conflict of Interest

The authors have no conflicts of interest regarding this investigation**.**

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