RECONSTRUCTION OF *Nannochloropsis oculata* PROTEIN-PROTEIN
INTERACTION NETWORK FOR GROWTH AND TRIACYLGLYCEROL
PRODUCTION

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RECONSTRUCTION OF *Nannochloropsis oculata* PROTEIN-PROTEIN INTERACTION NETWROK FOR GROWTH AND TRIACYLGLYCEROL PRODUCTION

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A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy (Bioscience)

Faculty of Science
Universiti Teknologi Malaysia

JANUARY 2019

SPECIALLY DEDICATED TO:

My *Abah*, Mahat bin Senon

My *Emak*, Habibah binti Hussein

My siblings:

Khamaliah, Kamaliana, Kamarudi, Kamisah dan Khairil Nizam

Brother and sister-in- laws:

Nazmi, Nur Hasanah, Mohd Zalman

ACKNOWLEDGEMENT

In the name of Allah, the Most Beneficent, the Most Merciful'

ABSTRACT

The aim of this study was to reconstruct protein-protein interaction map to allow researcher to identify pathway, biological roles and dynamic assembly of microalgae network pathways contributing to lipid production. The constructed PPI network was then characterised, and potential modifications were proposed based on this network to improve lipid production for mass biodiesel production. This bioinformatic approach is used to avoid the time consuming and expensive modification using high throughput approaches. In this study, literature search and data mining of rich information were interpreted into visualized outputs using Cystoscape. The outputs were then integrated and analysed to provide meaningful and reliable data. The study found that the constructed network consists of 153 nodes (proteins) and 1073 edges (interaction between proteins) with node degree R^2 coefficient distribution of 0.193 to exponent -0.387 denoting that the protein distributes randomly in the network and has clustering coefficient of 0.641 which was characterised by a highly connected node. The acyl-lipid (7-3)-desaturase (EDP09855) was identified as a bottleneck protein and a putative perturbation target for high quality biodiesel production. Cytoscape simulation and integration showed that alkaline growth conditions and phosphate and iron supplementation influenced PPI-directed pathway of *Chlamydomonas* sp. (model species) to glycerol lipid metabolism and fatty acid biosynthesis important for achieving high lipid productivity. In actual experimentation, microalgae *Nannochloropsis oculata* achieved highest percent of lipid yield when cultured in pH 8 growth conditions (3.45 %) or when growth was supplemented with 0.1 g/L phosphate (5.70 %) and 9.44 mg/L iron (6.21 %). Even though Cytoscape integration of three different vitamin B supplementation showed only minor possibility of pathway direction towards fatty acid biosynthesis in model species, maximum lipid productivity was achieved for *N. oculata* cultured using 500 µg/L biotin (4.98%), 50 µg/L thiamine (4.82%) and 0.5 µg/L cobalamin (7.59%). Altogether, computational biological pathway reconstruction positively supported network perturbations to optimize microalgae lipid productivity and actual experimentation validated the protein-protein network.

ABSTRAK

Tujuan kajian ini adalah untuk merangka semula peta interaksi protein-protein untuk membolehkan penyelidik mengenal pasti laluan, fungsi biologi dan rangkaian dinamik jejaring mikroalga yang menyumbang kepada pengeluaran lipid. Rangkaian PPI yang dibina kemudiannya dicirikan, dan pengubahsuaian yang berpotensi dicadangkan berdasarkan rangkaian ini untuk meningkatkan pengeluaran lipid bagi penghasilan biodiesel. Pendekatan bioinformatik ini digunakan untuk mengelakkan proses yang memakan masa yang lama dan kos yang tinggi dengan penggunaan pendekatan 'high throughput'. Dalam kajian ini, pencarian literatur dan perlombongan maklumat yang kaya ditafsirkan ke dalam hasil visual menggunakan 'Cystoscape'. Hasil ini kemudiannya diintegrasikan dan dianalisa untuk menghasilkan data yang bermakna dan boleh dipercayai. Kajian mendapati rangkaian yang dibina terdiri daripada 153 nod (protein) dan 1073 rangkaian (interaksi antara protein) dengan taburan koefisien darjah nod R^2 pada 0.193 hingga eksponen -0.387 menunjukkan bahawa protein tersusun secara rawak dalam rangkaian dan mempunyai pekali kluster 0.641 yang dicirikan oleh nod yang mempunyai hubungan tinggi. 'Acyl-lipid (7-3) - desaturase' (EDP09855) telah dikenal pasti sebagai protein cerutan dan sasaran pengubahsuaian untuk pengeluaran biodiesel yang berkualiti tinggi. Simulasi dan integrasi 'Cytoscape' menunjukkan bahawa keadaan pertumbuhan alkali dan suplemen fosfat dan zat besi mempengaruhi laluan yang diarahkan oleh PPI *Chlamydomonas* sp. (spesies model) ke metabolisme lipid gliserol dan biosintesis asid lemak yang penting untuk mencapai produktiviti lipid yang tinggi. Dalam eksperimen sebenar, mikroalga *Nannochloropsis oculata* mencapai peratusan tertinggi hasil lipid apabila dikulturkan dalam keadaan pertumbuhan pH 8 (3.45%) atau apabila pertumbuhan ditambah dengan 0.1 g/L fosfat (5.70%) dan 9.44 mg/L zat besi (6.21%). Walaupun integrasi 'Cytoscape' dari tiga jenis vitamin B yang berlainan menunjukkan hanya kemungkinan kecil arah jalur terarah ke biosintesis asid lemak dalam spesies model, produktiviti lipid maksimum *N. oculata* tercapai dengan menggunakan 500 µg/L biotin (4.98%), 50 µg/L tiamin (4.82%) dan 0.5 µg/L cobalamin (7.59%). Secara keseluruhannya, pembinaan semula laluan biologi komputasi menyokong pengubahsuaian rangkaian secara positif untuk mengoptimakan produktiviti lipid microalga dan eksperimen sebenar membuktikan rangkaian protein yang telah dibina adalah sah.

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LIST OF ABBREVIATIONS

PPI	-	Protein-protein interaction
KEGG	-	Kyoto Encyclopedia of Genes and Genomes
BLASTP	-	Basic Local Alignment Search Tool Protein
BLAST	-	Basic Local Alignment Search Tool
Tsv	-	Tab-separated values
DNA	-	deoxyribonucleic acid
UniProt	-	Universal Protein Knowledgebase
App	-	Application
API	-	Application programming interface
GO	-	Gene ontology
ATP	-	Adenosine triphosphate
NADPH	-	Nicotinamide adenine dinucleotide phosphate
RNA	-	Ribonucleic acid
FAME	-	Fatty acid methyl ester
TAG	-	Triacylglycerol
BC	-	Betweenness Centrality
CC	-	Closeness centrality
GC	-	Gas chromatography
CoA	-	Coenzyme A
ACP	-	Acyl carrier protein
DHAP	-	Dihydroxyacetone phosphate
GPAT	-	Glycerol-3-phosphate acyltransferase
PAP	-	Phosphatidic acid phosphatase

DAG	-	Diacylglycerol
LPAT	-	Lysophosphatidic acid acyl-transferase
DAGAT	-	Diacylglycerol acyltransferase
PDAT	-	Phospholipid: diacylglycerol transferase
TCA	-	Tricarboxylic acid
C	-	Carbon

LIST OF SYMBOLS

%	-	Percent
$\geq$	-	Less than and equal to
$\leq$	-	Higher than and equal to
$<$	-	Less than
$>$	-	Higher than
G	-	Gram
Mg	-	Milligram
L	-	Liter
g/L	-	Gram per liter
mg/L	-	Milligram per liter
µg/L	-	Microgram per liter
Ml	-	Milliliter
µM	-	Micrometer
v/v	-	Volume per volume
°C	-	Degree Celsius
Rpm	-	Rotation per minute
Ppt	-	Parts per thousand
R^2	-	R-squared
CO^2	-	Carbon dioxide
Ω	-	Omega
Vitamin B_1	-	Thiamine
Vitamin B_7	-	Biotin
Vitamin B_{12}	-	Cobalamin

div.day^{-1} -   Division per day

div/day   -   Division per day

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CHAPTER 1

INTRODUCTION

1.1   Background information

The functions of proteins are complicated because there is a hierarchal order in which proteins work with each other to form all sorts of biological processes and pathways. Understanding protein–protein interaction (PPI) can ease the discovery of existing interactions in organism as it is crucial for the revelation of protein functions and pathways in biological processes (Zahiri *et al.*, 2013). Such understanding can be achieved by high throughput methods such as the yeast two-hybrid method (Xing *et al.*, 2016). The results from PPI analysis can provide predictions of undiscovered protein complexes, hence enhancing the understanding of the underlying principles of the organisms' cellular organisation and also predicting plausible functions of a protein in a particular biological pathway (King *et al.*, 2004). However, genomics- and proteomics-based experimental methods for protein–protein interaction studies are often expensive and tedious and can be plagued with uncertainties and problems in reproducibility (Zahiri *et al.*, 2013).

Direct experimental method approaches for optimisation of biodiesel production are unfeasible due to the complex regulatory network and mutual interaction of the physiological processes involved that require longer time to achieve desirable outcome (Rupprecht, 2009). As alternatives, several computational methods based on gene neighbourhood, gene fusion, phylogeny, docking, co-expression, and

interologs are developed to understand the protein–protein interaction, causing the recent rise of the systems biology discipline in the field of bioinformatics (Rupprecht, 2009). These computational methods have emerged as powerful platforms for protein–protein interaction network build-up, integration, and analysis that can also be employed to validate experimental results (Zahiri *et al.*, 2013). Other than that, the ability to obtain information over a wide range of study framework and information gathered across species based on conserved protein sequences (Shen *et al.*, 2007) facilitates the protein–protein interaction network build-up. Protein–protein interaction analysis can give insights on how to enhance high quality microalgae lipid production by understanding the rich information of the protein–protein interaction involved in specific pathways inside the microalgae (Blatti *et al.*, 2012) because the biological pathway reconstruction can be done through wide range of physical and functional interaction (Muley and Ranjan, 2013) with possible alteration over different growth parameter implementation during cultivation. In addition, the protein-protein interaction dynamics and assembly causing the interaction to be more specific and for instance, one enzyme might favour a specific outcome meanwhile interactions between the enzyme with different partner might change the protein activity (Cesa *et al.*, 2015). The protein–protein interaction network prediction is plausible but there is a lack of evidence on protein–protein interaction network study on microalgae, which increases the chances of getting false positive results. This problem can be resolved by the employment of gene ontology annotation (Mahdavi and Lin, 2007) that mark the biological process of each protein in the network to identify the targeted protein.

Microalgae are the most potential feedstock for biodiesel production as their oil can exceed 80% of the dry cell weight (Chisti, 2007). *Nannochloropsis oculata*, which belongs to the Eustigmatophyte group, has received so much attention because this species is rich with fatty acid and can achieve lipid content of up to 60% of dry cell weight (Doan *et al.*, 2011), topping the chart as the most reliable species for biodiesel production. *Nannochloropsis oculata* lipid constituents consist of mainly neutral lipids (Huang *et al.*, 2014) that can be readily converted into high quality biodiesel. Biodiesel from microalgae is produce by the transesterification of triacylglycerol (microalgae storage lipid) to produce fatty acid methyl ester

(FAME/biodiesel) (Mubarak *et al.*, 2015). High quality biodiesel is characterised by a high cetane number value which indicates that the biodiesel has high ignition quality (Knothe *et al.*, 2003). Cetane number increases as the degree of the fatty acid saturation decreases and the number of carbon increases, but the number of carbon needs to be kept low enough to avoid increase in viscosity that will lead to biodiesel deposition during cold temperatures (Knothe, 2005).Highly saturated fatty acids such as palmitic acid methyl ester, myristic acid methyl ester, stearic acid methyl ester, and undecanoic acid methyl ester are favoured components in biodiesel production as it will produce biodiesel with high cetane number (Rasoul-Amini *et al.*, 2011) thus this had shown that microalgae should produce lipid that contain saturated or mon-unsaturated fatty acid to ensure that the lipid being converted to fatty acid methyl ester (biodiesel) during transesterification is favourable lipid for high-quality biodiesel production.

Microalgae lipid content can be controlled by modifying certain aspects such as their growth conditions or nutrient requirements, which will result in the increase of triglyceride production (Goncalves *et al.*, 2016) for instance alkaline environment, iron (Huang *et al.*, 2014) and vitamins (Neumara *et al.*, 2014) supplementation during growth causes increased accumulation of neutral lipid mainly saturated and monounsaturated fatty acids. Since algae lipid is expressed as the percentage of dry cell weight of the starting material, microalgae growth rate needs to be taken into consideration as lipid productivity will increase as the microalgae biomass increases. Studies have shown that iron (Sasireka and Muthuvelayudham, 2015) and vitamin supplementation (Li-xin *et al.*, 2013) and alkaline conditions (Difusa *et al.*, 2015) play important roles in triggering the increase of microalgae biomass. Reconstruction of biological pathway through wide range of physical or functional protein-protein interaction network prediction were made possible nowadays (Muley and Ranjan, 2013). There is growing body of knowledge stated that protein-protein interaction network were able to highlight the importance of microalgae pathway reconstruction for accelerating the development of commercially viable biodiesel production from algae biomass (Blatti *et al.*, 2012).Therefore, this study attempts to enhance the mass productivity of high-quality biodiesel by manipulating microalgae growth aspects and lipid enhancing parameter in silico by reconstruction of the microalgae biological

pathway with the establishment of protein-protein interaction network prediction that will be further validated by laboratory-scale experiments. This research will extend our knowledge with two main strategies which are to increase the desired lipid per unit biomass and to increase the biomass density to maximise biomass per culture volume or area with the assistance of the established protein–protein interaction network reconstruction.

1.2   Problem statement

Since 1970, microalgae have been shown to be a promising third generation source for biodiesel production that can be sustainably developed (John S. *et al.*, 1998). However, a lot of studies still need to be conducted to optimise the production of high-quality biodiesel to meet the global demand on energy consumption. The understanding of all cellular processes is possible with protein–protein interaction but understanding the protein–protein interaction by high-throughput methods is time consuming and far from being cost effective (Raman, 2010). Thus, in this study, the protein–protein interaction networks were reconstructed by using bioinformatics techniques since they are more economical, rapid, and convenient as proven by the study conducted by Han *et al.* (Han *et al.*, 2016). These in silico analyses provide data to help us understand the pathways involved in the growth and lipid production of microalgae so that these pathways can be targeted for modifications to enhance the microalgae growth and lipid production. As there is lack of experimental evidence to confirm the microalgae network reconstruction, the gene ontology annotation was employed to overcome the problem with the false positive outcomes (Ji et al., 2014).

1.3 Objectives

The objectives of this study are:

1. To mine and map protein–protein interaction network based on microalgae growth and triacylglycerol production and find the important node for putative perturbation target.

2. To identify the role of selected parameters in enhancing microalgae growth and triacylglycerol productivity through the established subnetwork.

3. To enhance the growth and microalgae triacylglycerol production and validate the established subnetwork through experimentation.

1.4 Scope of study

The study scope comprised the generation of candidate pathway of the network reconstruction in which various data sources were pooled together by using efficient text mining and literature mining procedure (Zahiri *et al.*, 2013) with the aid of tools such as Cytoscape plugins and open source databases. The data were then compiled, curated and filtered by using the STRING database (string-db.org) combined score (Szklarczyk *et al.*, 2017). The created protein–protein interaction network was visualised and integrated by using Cytoscape. The predicted protein–protein interaction network provide insight on the parameters for optimisation of *Nannochloropsis oculata* high quality biodiesel production. *Nannochloropsis oculata* was cultured under different growth parameter. Microalgae lipid was extracted and converted to biodiesel. Fatty acid profile was characterised by using gas chromatography.

1.5   Significances of study

      This study was carried out to promote microalgae growth and lipid productivity in which the protein-protein interaction map had reveals the possible protein interaction and major molecular functions association of genes involve in microalgae growth and triacyglycerol production. This study facilitates the optimization of microalgae growth and lipid productivity based on the reconstruction of biological pathway in the protein-protein interaction network with alteration on the pH of growth environment and nutrient supplementation such as iron, phosphate, biotin, thiamin and cobalamin supplementation on the microalgae growth media. This study indicates the feasibility of using protein–protein interaction network to reconstruct the biological pathway and guides specific experiments for researcher.

REFERENCES

Ahmad, A., Osman, S. M., Cha, T. S., and Loh, S. H. (2017). Phosphate-induced changes in fatty acid biosynthesis in *Chlorella* sp. KS-MA2 strain. *BioTechnologia*. 97(4), 295-304.

Ahmad, A. L., Yasin, N. H. M., Derek, C. J. C., and Lim, J. K. (2011). Microalgae as a sustainable energy source for biodiesel production: A review. *Renewable and Sustainable Energy Reviews*. 15(1), 584-593.

Allen, M. D., del Campo, J. A., Kropat, J., and Merchant, S. S. (2007). FEA1, FEA2, and FRE1, encoding two homologous secreted proteins and a candidate ferrireductase, are expressed coordinately with FOX1 and FTR1 in iron-deficient *Chlamydomonas reinhardtii*. *Eukaryot Cell*. 6(10), 1841-52.

Almaraz-Delgado, A. L., Flores-Uribe, J., Pérez-España, V. H., Salgado-Manjarrez, E., and Badillo-Corona, J. A. (2014). Production of therapeutic proteins in the chloroplast of *Chlamydomonas reinhardtii*. *AMB Express*. 4, 57-57.

Amaro, H. M., Guedes, A. C., and Malcata, F. X. (2011). Advances and perspectives in using microalgae to produce biodiesel. *Applied Energy*. 88(10), 3402-3410.

Anje, G., Elly, S., and Thomas, P. (2005). Effect of external pH on the growth, photosynthesis and photosynthetic electron transport of Chlamydomonas acidophila Negoro, isolated from an extremely acidic lake (pH 2.6). *Plant, Cell & Environment*. 28(10), 1218-1229.

Anthonisen, I. L., Salvador, M. L., and Klein, U. W. E. (2001). Specific sequence elements in the 5′ untranslated regions of rbcL and atpB gene mRNAs stabilize transcripts in the chloroplast of *Chlamydomonas reinhardtii*. *RNA*. 7(7), 1024-1033.

Apweiler, R., Bairoch, A., Wu, C. H., Barker, W. C., Boeckmann, B., Ferro, S., Gasteiger, E., Huang, H., Lopez, R., Magrane, M., Martin, M. J., Natale, D. A., O'Donovan, C., Redaschi, N., and Yeh, L.-S. L. (2004). UniProt: the Universal

Protein knowledgebase. *Nucleic Acids Research*. 32(Database issue), D115-D119.

Arriada, A. A., and Abreu, P. C. (2014). *Nannochloropsis oculata* growth in produced water: An alternatives for massive microalgae biomass production. *Brazilian Journal of petroleum and gas*. 8(3), 119-125.

Auchincloss, A. H., Zerges, W., Perron, K., Girard-Bascou, J., and Rochaix, J.-D. (2002). Characterization of Tbc2, a nucleus-encoded factor specifically required for translation of the chloroplast psbC mRNA in *Chlamydomonas reinhardtii*. *The Journal of Cell Biology*. 157(6), 953-962.

Avidan, O., Brandis, A., Rogachev, I., and Pick, U. (2015). Enhanced acetyl-CoA production is associated with increased triglyceride accumulation in the green alga *Chlorella desiccata*. *J Exp Bot*. 66.

Bader, G. D., Betel, D., and Hogue, C. W. V. (2003). BIND: the Biomolecular Interaction Network Database. *Nucleic Acids Res*. 31.

Bader, G. D., and Hogue, C. W. V. (2003). An automated method for finding molecular complexes in large protein interaction networks. *BMC Bioinformatics*. 4, 2-2.

Baicha, Z., Salar-García, M. J., Ortiz-Martínez, V. M., Hernández-Fernández, F. J., de los Ríos, A. P., Labjar, N., Lotfi, E., and Elmahi, M. (2016). A critical review on microalgae as an alternative source for bioenergy production: A promising low cost substrate for microbial fuel cells. *Fuel Processing Technology*. 154, 104-116.

Banerjee, S., Hew, W. E., Khatoon, H., Shariff, M., and Yusoff, F. M. (2011). Growth and proximate composition of tropical marine *Chaetoceros calcitrans* and *Nannochloropsis oculata* cultured outdoors and under laboratory conditions. *African Journal of Biotechnology*. 10(8), 1375-1383.

Barabási, A. L., and Oltvai, Z. N. (2004). Network biology: understanding the cell's functional organization. *Nat Rev Genet*. 5.

Barthélemy, M. (2004). Betweenness centrality in large complex networks. *The European Physical Journal B*. 38(2), 163-168.

Basso, S., Simionato, D., Gerotto, C., Segalla, A., Giacometti, G. M., and Morosinotto, T. (2014). Characterization of the photosynthetic apparatus of the Eustigmatophycean *Nannochloropsis gaditana*: Evidence of convergent

evolution in the supramolecular organization of photosystem I. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*. 1837(2), 306-314.

Battchikova, N., and Aro, E. M. (2007). Cyanobacterial NDH-1 complexes: multiplicity in function and subunit composition. *Physiol Plant*. 131(1), 22-32.

Beacham, T. A., Bradley, C., White, D. A., Bond, P., and Ali, S. T. (2014). Lipid productivity and cell wall ultrastructure of six strains of *Nannochloropsis*: Implications for biofuel production and downstream processing. *Algal Research* 6, 64-69.

Begley, T. P., Downs, D. M., Ealick, S. E., McLafferty, F. W., Van Loon, A. P. G. M., Taylor, S., Campobasso, N., Chiu, H.-J., Kinsland, C., Reddick, J. J., and Xi, J. (1999). Thiamin biosynthesis in prokaryotes. *Archives of Microbiology*. 171(5), 293-300.

Belotti, G., Bravi, M., de Caprariis, B., de Filippis, P., and Scarsella, M. (2013). Effect of nitrogen and phosphorus starvations on *Chlorella vulgaris* lipids productivity and quality under different trophic regimens for biodiesel production. *Am J Plant Sci*. 4, 44-51.

Bertrand, E. M., Allen, A. E., Dupont, C. L., Norden-Krichmar, T. M., Bai, J., Valas, R. E., and Saito, M. A. (2012). Influence of cobalamin scarcity on diatom molecular physiology and identification of a cobalamin acquisition protein. *Proceedings of the National Academy of Sciences*. 109(26), E1762–E1771.

Bibby, T. S., Nield, J., and Barber, J. (2001). Iron deficiency induces the formationof an antenna ring around trimeric photosystem I in cyanobacteria. *Nature*. 412(6848), 743-745.

Bigogno, C., Khozin-Goldberg, I., and Cohen, Z. (2002). Accumulation of arachidonic acid-rich triacylglycerols in the microalga *Parietochloris incisa* (Trebuxiophyceae, Chlorophyta). *Phytochemistry*. 60(2), 135-143.

Bindea, G., Mlecnik, B., Hackl, H., Charoentong, P., Tosolini, M., Kirilovsky, A., Fridman, W.-H., Pagès, F., Trajanoski, Z., and Galon, J. (2009). ClueGO: a Cytoscape plug-in to decipher functionally grouped gene ontology and pathway annotation networks. *Bioinformatics*. 25(8), 1091-1093.

Binns, D., Dimmer, E., Huntley, R., Barrell, D., O'Donovan, C., and Apweiler, R. (2009). QuickGO: a web-based tool for Gene Ontology searching. *Bioinformatics*. 25(22), 3045-3046.

Blanken, W., Postma, P. R., de Winter, L., Wijffels, R. H., and Janssen, M. (2016). Predicting microalgae growth. *Algal Research*. 14(Supplement C), 28-38.

Blaschke, C., Hoffmann, R., Oliveros, J. C., and Valencia, A. (2001). Extracting information automatically from biological literature. *Comparative and Functional Genomics*. 2(5), 310-313.

Blatti, J. L., Beld, J., Behnke, C. A., Mendez, M., Mayfield, S. P., and Burkart, M. D. (2012). Manipulating fatty acid biosynthesis in microalgae for biofuel through protein-protein interactions. *PLoS ONE*. 7(9), e42949.

Bojan, T., Supriya, G., Dale, T. R., Milan, S., Ross, M. L., Anthony, W. D. L., Jim, B. F., David, M. K., Susan, I. B., John, A. R., Martin, S., and Peter, J. R. (2014). The effect of diel temperature and light cycles on the growth of *Nannochloropsis oculata* in a photobioreactor matrix. *Plos one*. 9(1).

Bork, P., Jensen, L. J., von Mering, C., Ramani, A. K., Lee, I., and Marcotte, E. M. (2004). Protein interaction networks from yeast to human. *Current Opinion in Structural Biology*. 14(3), 292-299.

Borowitzka, M. A., Beardall, J., and Raven, J. A. (2016). *The Physiology of Microalgae*. (1). Switzerland: Springer International Publishing.

Bosque, G., Folch-Fortuny, A., Picó, J., Ferrer, A., and Elena, S. F. (2014). Topology analysis and visualization of *Potyvirus* protein-protein interaction network. *BMC Systems Biology*. 8(1), 129.

Botebol, H., Sutak, R., Scheiber, I. F., Blaiseau, P. L., Bouget, F. Y., Camadro, J. M., and Lesuisse, E. (2014). Different iron sources to study the physiology and biochemistry of iron metabolism in marine micro-algae. *Biometals*. 27.

Böttger, L. H., Miller, E. P., Andresen, C., Matzanke, B. F., Küpper, F. C., and Carrano, C. J. (2012). Atypical iron storage in marine brown algae: a multidisciplinary study of iron transport and storage in *Ectocarpus siliculosus*. *Journal of Experimental Botany*. 63(16), 5763-5772.

Boxers. George, E., and DeWitt Stetten, J. (1994). The role of thiamine in the synthesis of fatty acids from carbohydrate precursors. *The Journal of Biological Chemistry*. 153, 607-616.

Branco-Vieira, M., San-Martín, S., Agurto, C., A. Santos, M., Freitas, M., and Caetano, N. (2017). *Analyzing Phaeodactylum tricornutum lipid profile for biodiesel production*.

Brandes, U. (2001). A faster algorithm for betweenness centrality. *The Journal of Mathematical Sociology*. 25(2), 163-177.

Breil, C., Abert Vian, M., Zemb, T., Kunz, W., and Chemat, F. (2017). "Bligh and Dyer" and Folch Methods for Solid–Liquid–Liquid Extraction of Lipids from Microorganisms. Comprehension of Solvatation Mechanisms and towards Substitution with Alternative Solvents. *International Journal of Molecular Sciences*. 18(4), 708.

Brückner, A., Polge, C., Lentze, N., Auerbach, D., and Schlattner, U. (2009). Yeast two-hybrid, a powerful tool for systems biology. *International Journal of Molecular Sciences*. 10(6), 2763-2788.

Brun, C., Chevenet, F., Martin, D., Wojcik, J., Guénoche, A., and Jacq, B. (2003). Functional classification of proteins for the prediction of cellular function from a protein-protein interaction network. *Genome Biology*. 5(1), R6.

Bu, D., Zhao, Y., Cai, L., Xue, H., Zhu, X., Lu, H., Zhang, J., Sun, S., Ling, L., Zhang, N., Li, G., and Chen, R. (2003). Topological structure analysis of the protein–protein interaction network in budding yeast. *Nucleic Acids Research*. 31(9), 2443-2450.

Camon, E., Magrane, M., Barrell, D., Lee, V., Dimmer, E., Maslen, J., Binns, D., Harte, N., Lopez, R., and Apweiler, R. (2004). The Gene Ontology Annotation (GOA) Database: sharing knowledge in Uniprot with Gene Ontology. *Nucleic Acids Research*. 32(Database issue), D262-D266.

Cardol, P., Forti, G., and Finazzi, G. (2011). Regulation of electron transport in microalgae. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*. 1807(8), 912-918.

Cesa, L. C., Mapp, A. K., and Gestwicki, J. E. (2015). Direct and propagated effects of small molecules on protein–protein interaction networks. *Frontiers in Bioengineering and Biotechnology*. 3, 119.

Chader, S., Mahmah, B., Chetehouna, K., Amrouche, F., and Abdeladim, K. (2011). Biohydrogen production using green microalgae as an approach to operate a small proton exchange membrane fuel cell. *International Journal of Hydrogen Energy*. 36(6), 4089-4093.

Chapman, S. P., Trindade dos Santos, M., Johnson, G. N., Kritz, M. V., and Schwartz, J.-M. (2017). Cyclic decomposition explains a photosynthetic down regulation for *Chlamydomonas reinhardtii*. *Biosystems*. 162, 119-127.

Chen, H., and Sharp, B. M. (2004). Content-rich biological network constructed by mining PubMed abstracts. *BMC Bioinformatics*. 5(1), 147.

Chen, J. E., and Smith, A. G. (2012). A look at diacylglycerol acyltransferases (DGATs) in algae. *J Biotechnol*. 162.

Chisti, Y. (2007). Biodiesel from microalgae. *Biotechnology Advances*. 25(3), 294-306.

Chisti, Y. (2008). Biodiesel from microalgae beats bioethanol. *Trends in Biotechnology*. 26(3), 126-131.

Chiu, S. Y., Kao, C. Y., Tsai, M. T., Ong, S. C., Chen, C. H., and Lin, C. S. (2009). Lipid accumulation and CO_2 utilization of *Nannochloropsis oculata* in response to CO_2 aeration. *Bioresource Technol*. 100(2), 833-838.

Chung, C.-C., Hwang, S.-P. L., and Chang, J. (2003). Identification of a high-affinity phosphate transporter gene in a prasinophyte alga, *Tetraselmis chui*, and its expression under nutrient limitation. *Applied and Environmental Microbiology*. 69(2), 754-759.

Converti, A., Casazza, A. A., Ortiz, E. Y., Perego, P., and Del, B. M. (2009). Effect of temperature and nitrogen concentration on the growth and lipid content of *Nannochloropsis oculata* and *Chlorella vulgaris* for biodiesel production. *Chem Eng Process*. 48(6), 1146-1151.

Couto, R. M., Simões, P. C., Reis, A., Da Silva, T. L., Martins, V. H., and Sánchez-Vicente, Y. (2010). Supercritical fluid extraction of lipids from the heterotrophic microalga *Crypthecodinium cohnii*. *Engineering in Life Sciences*. 10(2), 158-164.

Cravotto, G., Boffa, L., Mantegna, S., Perego, P., Avogadro, M., and Cintas, P. (2008). Improved extraction of vegetable oils under high-intensity ultrasound and/or microwaves. *Ultrasonics Sonochemistry*. 15(5), 898-902.

Croft, M. T., Lawrence, A. D., Raux-Deery, E., Warren, M. J., and Smith, A. G. (2005). Algae acquire vitamin B12 through a symbiotic relationship with bacteria. *Nature*. 438(7064), 90-93.

Croft, M. T., Warren, M. J., and Smith, A. G. (2006). Algae need their vitamins. *Eukaryot Cell*. 5(8), 1175-83.

Cronan, J. E., and Waldrop, G. L. (2002). Multi-subunit acetyl-CoA carboxylases. *Prog Lipid Res*. 41.

Dahlqvist, A., Ståhl, U., Lenman, M., Banas, A., Lee, M., Sandager, L., Ronne, H., and Stymne, S. (2000). Phospholipid:diacylglycerol acyltransferase: An enzyme that catalyzes the acyl-CoA-independent formation of triacylglycerol in yeast and plants. *Proceedings of the National Academy of Sciences*. 97(12), 6487-6492.

Davis, M. S., Solbiati, J., and Cronan, J. E. (2000). Overproduction of acetyl-CoA carboxylase activity increases the rate of fatty acid biosynthesis in *Escherichia coli*. *J Biol Chem*. 275.

De, S., and Babu, M. M. (2010). Genomic neighbourhood and the regulation of gene expression. *Curr Opin Cell Biol*. 22(3), 326-33.

Dhup, S., Kannan, D. C., and Dhawan, V. Growth, lipid productivity and cellular mechanism of lipid accumulation in microalgae *Monoraphidium* sp. following different phosphorous concentrations for biofuel production. *Current Science*. 112(3), 539-548.

Diaz-Beltran, L., Cano, C., Wall, D. P., and Esteban, F. J. (2013). Systems biology as a comparative approach to understand complex gene expression in neurological diseases. *Behav Sci (Basel)*. 3(2), 253-72.

Difusa, A., Talukdar, J., Kalita, M. C., Mohanty, K., and Goud, V. V. (2015). Effect of light intensity and pH condition on the growth, biomass and lipid content of microalgae *Scenedesmus* species. *Biofuels*. 6(1-2), 37-44.

Dinc, E., Ramundo, S., Croce, R., and Rochaix, J.-D. (2014). Repressible chloroplast gene expression in *Chlamydomonas*: A new tool for the study of the photosynthetic apparatus. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*. 1837(9), 1548-1552.

Doan, T. T. Y., Sivaloganathan, B., and Obbard, J. P. (2011). Screening of marine microalgae for biodiesel feedstock. *Biomass Bioenerg*. 35(7), 2534-2544.

Doetsch, N. A., Favreau, M. R., Kuscuoglu, N., Thompson, M. D., and Hallick, R. B. (2001). Chloroplast transformation in Euglena gracilis: splicing of a group III twintron transcribed from a transgenic psbK operon. *Curr Genet*. 39(1), 49-60.

Doms, A., and Schroeder, M. (2005). GoPubMed: exploring PubMed with the Gene Ontology. *Nucleic Acids Res*. 33(Web Server issue), W783-6.

Duanmu, D., Casero, D., Dent, R. M., Gallaher, S., Yang, W., Rockwell, N. C., Martin, S. S., Pellegrini, M., Niyogi, K. K., Merchant, S. S., Grossman, A. R., and Lagarias, J. C. (2013). Retrograde bilin signaling enables *Chlamydomonas* greening and phototrophic survival. *Proceedings of the National Academy of Sciences*. 110(9), 3621-3626.

Dyhrman, S. T., Chappell, P. D., Haley, S. T., Moffett, J. W., Orchard, E. D., Waterbury, J. B., and Webb, E. A. (2006). Phosphonate utilization by the globally important marine diazotroph *Trichodesmium*. *Nature*. 439(7072), 68-71.

Eckardt, N. A. (2001). A Role for *PsbZ* in the Core Complex of Photosystem II. *The Plant Cell*. 13(6), 1245-1248.

Edwards, A. M., Kus, B., Jansen, R., Greenbaum, D., Greenblatt, J., and Gerstein, M. (2002). Bridging structural biology and genomics: assessing protein interaction data with known complexes. *Trends Genet*. 18(10), 529-36.

Edwards, J. S., Ibarra, R. U., and Palsson, B. O. (2001). In silico predictions of *Escherichia coli* metabolic capabilities are consistent with experimental data. *Nature Biotechnology*. 19, 125.

El Gamal, A. A. (2010). Biological importance of marine algae. *Saudi Pharmaceutical Journal : SPJ*. 18(1), 1-25.

Estevez, M. S., Malanga, G., and Puntarulo, S. (2001). Iron-dependent oxidative stress in *Chlorella vulgaris*. *Plant Sci*. 161(1), 9-17.

Estrada, E., and Rodríguez-Velázquez, J. A. (2005). Subgraph centrality in complex networks. *Physical Review E*. 71(5), 056103.

Fakas, S., Konstantinou, C., and Carman, G. M. (2011). DGK1-encoded diacylglycerol kinase activity is required for phospholipid synthesis during growth resumption from stationary phase in *Saccharomyces cerevisiae*. *J Biol Chem*. 286(2), 1464-74.

Fan, J., Andre, C., and Xu, C. (2011). A chloroplast pathway for the *de novo* biosynthesis of triacylglycerol in *Chlamydomonas reinhardtii*. *FEBS Lett*. 585.

Fan, J., Cui, Y., Wan, M., Wang, W., and Li, Y. (2014). Lipid accumulation and biosynthesis genes response of the oleaginous Chlorella pyrenoidosaunder three nutrition stressors. *Biotechnology for Biofuels*. 7(1), 17.

Fang, W., Si, Y., Douglass, S., Casero, D., Merchant, S. S., Pellegrini, M., Ladunga, I., Liu, P., and Spalding, M. H. (2012). Transcriptome-wide changes in *Chlamydomonas reinhardtii* gene expression regulated by carbon dioxide and the CO_2-concentrating mechanism regulator CIA5/CCM1. *The Plant Cell*. 24(5), 1876-1893.

Feng, P., Deng, Z., Fan, L., and Hu, Z. (2012). Lipid accumulation and growth characteristics of Chlorella zofingiensis under different nitrate and phosphate concentrations. *J Biosci Bioeng*. 114.

Forti, G., Furia, A., Bombelli, P., and Finazzi, G. (2003). In vivo changes of the oxidation-reduction state of NADP and of the ATP/ADP cellular ratio linked to the photosynthetic activity in *Chlamydomonas reinhardtii*. *Plant physiology*. 132(3), 1464-1474.

Franceschini, A., Szklarczyk, D., Frankild, S., Kuhn, M., Simonovic, M., Roth, A., Lin, J., Minguez, P., Bork, P., von Mering, C., and Jensen, L. J. (2013). STRING v9.1: protein-protein interaction networks, with increased coverage and integration. *Nucleic Acids Research*. 41(D1), D808-D815.

Fu, L., Cui, X., Li, Y., Xu, L., Zhang, C., Xiong, R., Zhou, D., and Crittenden, J. C. (2017). Excessive phosphorus enhances *Chlorella regularis* lipid production under nitrogen starvation stress during glucose heterotrophic cultivation. *Chemical Engineering Journal*. 330, 566-572.

Fukuda, H., Kondo, A., and Noda, H. (2001). Biodiesel fuel production by transesterification of oils. *Journal of Bioscience and Bioengineering*. 92(5), 405-416.

Fuszard, M. A., Ow, S. Y., Gan, C. S., Noirel, J., Ternan, N. G., McMullan, G., Biggs, C. A., Reardon, K. F., and Wright, P. C. (2013). The quantitative proteomic response of Synechocystis sp. PCC6803 to phosphate acclimation. *Aquatic Biosystems*. 9, 5-5.

Galagan, J. E., Calvo, S. E., Borkovich, K. A., Selker, E. U., Read, N. D., Jaffe, D., FitzHugh, W., Ma, L.-J., Smirnov, S., Purcell, S., Rehman, B., Elkins, T., Engels, R., Wang, S., Nielsen, C. B., Butler, J., Endrizzi, M., Qui, D., Ianakiev,

P., Bell-Pedersen, D., Nelson, M. A., Werner-Washburne, M., Selitrennikoff, C. P., Kinsey, J. A., Braun, E. L., Zelter, A., Schulte, U., Kothe, G. O., Jedd, G., Mewes, W., Staben, C., Marcotte, E., Greenberg, D., Roy, A., Foley, K., Naylor, J., Stange-Thomann, N., Barrett, R., Gnerre, S., Kamal, M., Kamvysselis, M., Mauceli, E., Bielke, C., Rudd, S., Frishman, D., Krystofova, S., Rasmussen, C., Metzenberg, R. L., Perkins, D. D., Kroken, S., Cogoni, C., Macino, G., Catcheside, D., Li, W., Pratt, R. J., Osmani, S. A., DeSouza, C. P. C., Glass, L., Orbach, M. J., Berglund, J. A., Voelker, R., Yarden, O., Plamann, M., Seiler, S., Dunlap, J., Radford, A., Aramayo, R., Natvig, D. O., Alex, L. A., Mannhaupt, G., Ebbole, D. J., Freitag, M., Paulsen, I., Sachs, M. S., Lander, E. S., Nusbaum, C., and Birren, B. (2003). The genome sequence of the filamentous fungus Neurospora crassa. *Nature*. 422, 859.

Gasparini, F., Lima, J., A. Ghani, Y., Hatanaka, R., Sequinel, R., Flumignan, D., and de Oliveira, J. E. (2011). *EN 14103 Adjustments for biodiesel analysis from different raw materials, including animal tallow containing C17*.

Geider, R. J., La Roche, J., Greene, R. M., and Olaizola, M. (1993). Response of the photosynthetic apparatus of *Phaeodactylum tricornutum* (Bacillariophyceae) to nitrate, phosphate or iron starvation *Journal of Phycology*. 29(6), 755-766.

Gerloff-Elias, A., Spijkerman, E., and PrÖSchold, T. (2005). Effect of external pH on the growth, photosynthesis and photosynthetic electron transport of Chlamydomonas acidophila Negoro, isolated from an extremely acidic lake (pH 2.6). *Plant, Cell & Environment*. 28(10), 1218-1229.

Gibellini, F., and Smith, T. K. (2010). The Kennedy pathway--De novo synthesis of phosphatidylethanolamine and phosphatidylcholine. *IUBMB Life*. 62(6), 414-28.

Giuliano, S., Agata, P., Anuta, C., Massimiliano, G., Maura, B., and Efisio Antonio, S. (2016). Study of the growth parameters of the *Nannochloropsis Oculata* for the nitrogen and phosphorus removal from wastewater through design of experiment approach *Chemical engineering transactions*. 49, 553-558.

Goh, C. S., and Cohen, F. E. (2002). Co-evolutionary analysis reveals insights into protein-protein interactions. *J Mol Biol*. 324.

Goldberg, S. (2008). Mechanical/Physical Methods of Cell Disruption and Tissue Homogenization. In Posch, A. (Ed.) *2D PAGE: Sample Preparation and Fractionation* (pp. 3-22). Totowa, NJ: Humana Press.

Gómez, G., Pikal, M. J., and Rodríguez-Hornedo, N. (2001). Effect of Initial Buffer Composition on pH Changes During Far-From-Equilibrium Freezing of Sodium Phosphate Buffer Solutions. *Pharmaceutical Research*. 18(1), 90-97.

Goncalves, E. C., Wilkie, A. C., Kirst, M., and Rathinasabapathi, B. (2016). Metabolic regulation of triacylglycerol accumulation in the green algae: identification of potential targets for engineering to improve oil yield. *Plant Biotechnol J*. 14(8), 1649-60.

Goo, Y. A., Roach, J., Glusman, G., Baliga, N. S., Deutsch, K., Pan, M., Kennedy, S., DasSarma, S., Victor Ng, W., and Hood, L. (2004). Low-pass sequencing for microbial comparative genomics. *BMC Genomics*. 5, 3-3.

Greene, C. S., and Troyanskaya, O. G. (2010). Integrative systems biology for data driven knowledge discovery. *Seminars in nephrology*. 30(5), 443-454.

Grossman, A. R., Harris, E. E., Hauser, C., Lefebvre, P. A., Martinez, D., Rokhsar, D., Shrager, J., Silflow, C. D., Stern, D., Vallon, O., and Zhang, Z. (2003). *Chlamydomonas reinhardtii* at the crossroads of genomics. *Eukaryotic Cell*. 2(6), 1137-1150.

Grossman, A. R., Karpowicz, S. J., Heinnickel, M., Dewez, D., Hamel, B., Dent, R., Niyogi, K. K., Johnson, X., Alric, J., Wollman, F.-A., Li, H., and Merchant, S. S. (2010). Phylogenomic analysis of the *Chlamydomonas* genome unmasks proteins potentially involved in photosynthetic function and regulation. *Photosynthesis Research*. 106(1), 3-17.

Gu, N., Lin, Q., Li, G., Tan, Y., Huang, L., and Lin, J. (2012). Effect of salinity on growth, biochemical composition, and lipid productivity of Nannochloropsis oculataCS 179. *Engineering in Life Sciences*. 12(6), 631-637.

Gursoy, A., Keskin, O., and Nussinov, R. (2008). Topological properties of protein interaction networks from a structural perspective. *Biochem Soc Trans*. 36(Pt 6), 1398-403.

Guschina, I. A., and Harwood, J. L. (2006). Lipids and lipid metabolism in eukaryotic algae. *Progress in Lipid Research*. 45(2), 160-186.

Hakenberg, J., Nenadic, G., Rebholz-Schuhmann, D., and Kim, J.-D. (2013). Literature Mining Solutions for Life Science Research. *Advances in Bioinformatics*. 2013, 320436.

Hannon, M., Gimpel, J., Tran, M., Rasala, B., and Mayfield, S. (2010). Biofules from algae: challenges and potential. *Biofuels*. 1(5), 763-784.

Hashemifar, S., Neyshabur, B., Khan, A. A., and Xu, J. (2018). Predicting protein–protein interactions through sequence-based deep learning. *Bioinformatics*. 34(17), i802-i810.

Hatano-Iwasaki, A., Minagawa, J., Inoue, Y., and Takahashi, Y. (2000). Characterization of chloroplast psbA transformants of *Chlamydomonas reinhardtii* with impaired processing of a precursor of a photosystem II reaction center protein, D1. *Plant Mol Biol*. 42(2), 353-63.

Havlík, P., Schneider, U. A., Schmid, E., Böttcher, H., Fritz, S., Skalský, R., Aoki, K., Cara, S. D., Kindermann, G., Kraxner, F., Leduc, S., McCallum, I., Mosnier, A., Sauer, T., and Obersteiner, M. (2011). Global land-use implications of first and second generation biofuel targets. *Energy Policy*. 39(10), 5690-5702.

Helliwell, K. E., Scaife, M. A., Sasso, S., Araujo, A. P., Purton, S., and Smith, A. G. (2014). Unraveling vitamin B12-responsive gene regulation in algae. *Plant Physiol*. 165(1), 388-97.

Helliwell, K. E., Wheeler, G. L., Leptos, K. C., Goldstein, R. E., and Smith, A. G. (2011). Insights into the Evolution of Vitamin B12 Auxotrophy from Sequenced Algal Genomes. *Molecular Biology and Evolution*. 28(10), 2921-2933.

Herland, M., Khoshgoftaar, T. M., and Wald, R. (2014). A review of data mining using big data in health informatics. *Journal Of Big Data*. 1(1), 2.

Herrera-Valencia, V. A., Macario-González, L. A., Casais-Molina, M. L., Beltran-Aguilar, A. G., and Peraza-Echeverría, S. (2012). In silico cloning and characterization of the glycerol-3-phosphate dehydrogenase (GPDH) gene family in the green microalga Chlamydomonas reinhardtii. *Curr Microbiol*. 64.

Higgins, B. T., Wang, Q., Du, S., Hennebelle, M., Taha, A. Y., Fiehn, O., and VanderGheynst, J. S. (2018). Impact of thiamine metabolites and spent medium from *Chlorella sorokiniana* on metabolism in the green algae *Auxenochlorella prototheciodes*. 33, 197-208.

Hirschman, L., Park, J. C., Tsujii, J., Wong, L., and Wu, C. H. (2002). Accomplishments and challenges in literature data mining for biology. *Bioinformatics*. 18(12), 1553-1561.

Hodson, S., Croft, M., Deery, E., Smith, A., and Warren, M. (2007). Algae acquire Vitamin B12 through a symbiotic relationship with bacteria. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*. 146(4, Supplement), S222.

Hosseinpour, B., HajiHoseini, V., Kashfi, R., Ebrahimie, E., and Hemmatzadeh, F. (2012). Protein Interaction Network of Arabidopsis thaliana Female Gametophyte Development Identifies Novel Proteins and Relations. *PLOS ONE*. 7(12), e49931.

Hu, H., and Gao, K. (2003). Optimization of growth and fatty acid composition of a unicellular marine picoplankton, Nannochloropsis sp., with enriched carbon sources. *Biotechnology Letters*. 25(5), 421-425.

Huang, H., Alvarez, S., and Nusinow, D. A. (2016). Data on the identification of protein interactors with the Evening Complex and PCH1 in *Arabidopsis* using tandem affinity purification and mass spectrometry (TAP–MS). *Data in Brief*. 8, 56-60.

Huang, X., Wei, L., Huang, Z., and Yan, J. (2014). Effect of high ferric ion concentrations on total lipids and lipid characteristics of *Tetraselmis subcordiformis*, *Nannochloropsis oculata* and *Pavlova viridis*. *J Appl Phycol*. 26(1), 105-114.

Hwang, S., Son, S. W., Kim, S. C., Kim, Y. J., Jeong, H., and Lee, D. (2008). A protein interaction network associated with asthma. *J Theor Biol*. 252(4), 722-31.

Iriani, D., Suriyaphan, O., and Chaiyanate, N. (2011). Effect of iron concentration on growth, protein and total phenolic content of *Chlorella* sp. cultured in basal medium. *Sains Malaysiana*. 40(4), 363-358.

Ito, T., Chiba, T., Ozawa, R., Yoshida, M., Hattori, M., and Sakaki, Y. (2001). A comprehensive two-hybrid analysis to explore the yeast protein interactome. *Proc Natl Acad Sci USA*. 98.

Jalal, A., Schwarz, C., Schmitz-Linneweber, C., Vallon, O., Nickelsen, J., and Bohne, A.-V. (2015). A small multifunctional pentatricopeptide repeat protein in the chloroplast of *Chlamydomonas reinhardtii*. *Molecular Plant*. 8(3), 412-426.

Jason, C. Q., Tracy, Y., Nathaniel, D., Kristina, W., Joel, B., Thiomas, H. B., and Peter, J. L. (2012). *Nannochloropsis oculata* production metrics in a scalable outdoor photobioreactor for commercial applications. *Bioresource Technology*. 164-171.

Jensen, L. J., Saric, J., and Bork, P. (2007). Literature mining for the biologist: from information retrieval to biological discovery. *Nature Reviews Genetics*. 7(119–129).

Jin, B., Li, Y., and Robertson, K. D. (2011). DNA Methylation: Superior or Subordinate in the Epigenetic Hierarchy? *Genes & Cancer*. 2(6), 607-617.

Jin, H.-H., and Jiang, J.-G. (2015). Phosphatidic Acid Phosphatase and Diacylglycerol Acyltransferase: Potential Targets for Metabolic Engineering of Microorganism Oil. *Journal of Agricultural and Food Chemistry*. 63(12), 3067-3077.

John S., Terri D., John B., and R., P. 1998. A look back at the U.S. Department of Energy's Aquatic Species Program:Biodiesel from algae. Colorado: A national laboratory of the U.S. Department of Energy.

Joshi, T., and Xu, D. (2007). Quantitative assessment of relationship between sequence similarity and function similarity. *BMC Genomics*. 8, 222-222.

Juneja, A., Ceballos, R., and Murthy, G. (2013). Effects of environmental factors and nutrient availability on the biochemical composition of algae for biofuels production: A review. *Energies*. 6(9), 4607.

Jurgenson, C. T., Begley, T. P., and Ealick, S. E. (2009). The structural and biochemical foundations of thiamin biosynthesis. *Annu Rev Biochem*. 78, 569-603.

Kagan, M. L., and Matulka, R. A. (2015). Safety assessment of the microalgae *Nannochloropsis oculata*. *Toxicology Reports*. 2, 617-623.

Kalhan, S. C. (2013). One Carbon Metabolism, Fetal Growth and Long Term Consequences. *Nestle Nutrition Institute workshop series*. 74, 127-138.

Kalpesh, K. S., Holger, S., and Peer, M. S. (2012). High lipid induction in microalgae for biodiesel production. *Journal Energies*. 5, 1532-1553.

Kanehisa, M., and Goto, S. (2000). KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research*. 28(1), 27-30.

Kaplan, A., and Reinhold, L. (1999). CO$_2$ Concentrating mechanisms in photosynthetic microorganism *Annu Rev Plant Physiol Plant Mol Biol*. 50, 539-570.

Kawakami, K., Umena, Y., Iwai, M., Kawabata, Y., Ikeuchi, M., Kamiya, N., and Shen, J.-R. (2011). Roles of *Psb*I and *PsbM* in photosystem II dimer formation and stability studied by deletion mutagenesis and X-ray crystallography. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*. 1807(3), 319-325.

Ke, J., Behal, R. H., Back, S. L., Nikolau, B. J., Wurtele, E. S., and Oliver, D. J. (2000). The Role of Pyruvate Dehydrogenase and Acetyl-Coenzyme A Synthetase in Fatty Acid Synthesis in Developing Arabidopsis Seeds. *Plant Physiology*. 123(2), 497-508.

Khozin-Goldberg, I., and Cohen, Z. (2006). The effect of phosphate starvation on the lipid and fatty acid composition of the fresh water eustigmatophyte Monodus subterraneus. *Phytochemistry*. 67(7), 696-701.

Khozin-Goldberg, I., and Cohen, Z. (2011). Unraveling algal lipid metabolism: Recent advances in gene identification. *Biochimie*. 93(1), 91-100.

King, A. D., Pržulj, N., and Jurisica, I. (2004). Protein complex prediction via cost-based clustering. *Bioinformatics*. 20(17), 3013-3020.

Knothe, G. (2005). Dependence of biodiesel fuel properties on the structure of fatty acid alkyl esters. *Fuel Processing Technology*. 86(10), 1059-1070.

Knothe, G., Matheaus, A. C., and Ryan Iii, T. W. (2003). Cetane numbers of branched and straight-chain fatty esters determined in an ignition quality tester☆. *Fuel*. 82(8), 971-975.

Kos, P. B., Deak, Z., Cheregi, O., and Vass, I. (2008). Differential regulation of *psbA* and *psbD* gene expression, and the role of the different D1 protein copies in the *cyanobacterium Thermosynechococcus elongatus* BP-1. *Biochim Biophys Acta*. 1777(1), 74-83.

Krallinger, M., Erhardt, R. A.-A., and Valencia, A. (2005). Text-mining approaches in molecular biology and biomedicine. *Drug Discovery Today*. 10(6), 439-445.

Kramzar, L. M., Mueller, T., Erickson, B., and Higgs, D. C. (2006). Regulatory sequences of orthologous petD chloroplast mRNAs are highly specific among *Chlamydomonas* species. *Plant Molecular Biology*. 60(3), 405-422.

Kruskopf, M. M., and Du Plessis, S. (2004). Induction of both acid and alkaline phosphatase activity in two green-algae (chlorophyceae) in low N and P concentrations. *Hydrobiologia*. 513(1), 59-70.

Kunze, M., Pracharoenwattana, I., Smith, S. M., and Hartig, A. (2006). A central role for the peroxisomal membrane in glyoxylate cycle function. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*. 1763(12), 1441-1452.

Kurotani, A., Yamada, Y., and Sakurai, T. (2017). Alga-PrAS (Algal Protein Annotation Suite): A Database of Comprehensive Annotation in Algal Proteomes. *Plant Cell Physiol*. 58(1), e6.

Lapaille, M., Thiry, M., Perez, E., Gonzalez-Halphen, D., Remacle, C., and Cardol, P. (2010). Loss of mitochondrial ATP synthase subunit beta (*Atp2*) alters mitochondrial and chloroplastic function and morphology in *Chlamydomonas*. *Biochim Biophys Acta*. 1797(8), 1533-9.

Lee, J. Y., Yoo, C., Jun, S. Y., Ahn, C. Y., and Oh, H. M. (2010). Comparison of several methods for effective lipid extraction from microalgae. *Bioresource Technology*. 101(1), S75-S77.

Lehninger, A. (1975). Biochemistry Worth. *New York*. 176.

Lelandais, G., Scheiber, I., Paz-Yepes, J., Lozano, J.-C., Botebol, H., Pilátová, J., Žárský, V., Léger, T., Blaiseau, P.-L., Bowler, C., Bouget, F.-Y., Camadro, J.-M., Sutak, R., and Lesuisse, E. (2016). Ostreococcus tauri is a new model green alga for studying iron metabolism in eukaryotic phytoplankton. *BMC Genomics*. 17(1), 319.

Leung, D. Y. C., Wu, X., and Leung, M. K. H. (2010). A review on biodiesel production using catalyzed transesterification. *Applied Energy*. 87(4), 1083-1095.

Li-Beisson, Y., Beisson, F., and Riekhof, W. (2015). Metabolism of acyl-lipids in Chlamydomonas reinhardtii. *Plant J*. 82(3), 504-22.

Li-Beisson, Y., Shorrosh, B., Beisson, F., Andersson, M. X., Arondel, V., Bates, P. D., Baud, S., Bird, D., DeBono, A., Durrett, T. P., Franke, R. B., Graham, I. A., Katayama, K., Kelly, A. A., Larson, T., Markham, J. E., Miquel, M., Molina, I., Nishida, I., Rowland, O., Samuels, L., Schmid, K. M., Wada, H., Welti, R., Xu, C., Zallot, R., and Ohlrogge, J. (2010). Acyl-Lipid Metabolism. *The Arabidopsis Book / American Society of Plant Biologists*. 8, e0133.

Li-xin, L., Zhi-wei, S., You, Z., Shun-shan, D., Qian-shen, Z., and Yan, L. (2013). Effect of Vitamin-B12 and Vitamin-H on the Growth and Astaxanthin Content of *Haematococcus pluvialis CH-1 Advance Journal of Food Science and Technology* 5(9), 1139-1142.

Li, J., Han, D., Wang, D., Ning, K., Jia, J., and Wei, L. (2014). Choreography of transcriptomes and lipidomes of nannochloropsis reveals the mechanisms of oil synthesis in microalgae. *Plant Cell*. 26.

Li, X., Wu, M., Kwoh, C. K., and Ng, S. K. (2010). Computational approaches for detecting protein complexes from protein interaction networks: a survey. *BMC Genomics*. 11 Suppl 1, S3.

Liang, K., Zhang, Q., Gu, M., and Cong, W. (2013). Effect of phosphorus on lipid accumulation in freshwater microalga *Chlorella sp*. *Journal of Applied Phycology*. 25(1), 311-318.

Liepe, J., Filippi, S., Komorowski, M., and Stumpf, M. P. H. (2013). Maximizing the information content of experiments in systems biology. *PLOS Computational Biology*. 9(1), e1002888.

Lin, C., Cho, Y.-R., Hwang, W.-C., Pei, P., and Zhang, A. (2007). Clustering Methods in a Protein–Protein Interaction Network. *Knowledge Discovery in Bioinformatics* (pp. 319-355). John Wiley & Sons, Inc.

Lin, M., and Oliver, D. J. (2008). The role of acetyl-coenzyme a synthetase in Arabidopsis. *Plant Physiol*. 147.

Liu, H., Huang, D., and Wen, J. (2016). Integrated intracellular metabolic profiling and pathway analysis approaches reveal complex metabolic regulation by Clostridium acetobutylicum. *Microbial Cell Factories*. 15, 36.

Liu, J., Chakraborty, S., Hosseinzadeh, P., Yu, Y., Tian, S., Petrik, I., Bhagi, A., and Lu, Y. (2014a). Metalloproteins containing cytochrome, iron–sulfur, or copper redox centers. *Chemical Reviews*. 114(8), 4366-4469.

Liu, Z., and Wang, G. (2014). Effect of Fe^{3+} on the growth and lipid content of *Isochrysis galbana*. *Chinese Journal of Oceanology and Limnology*. 32(1), 47-53.

Liu, Z. Y., Wang, G. C., and Zhou, B. C. (2008). Effect of iron on growth and lipid accumulation in *Chlorella vulgaris*. *Bioresource Technology*. 99(11), 4717-4722.

Liu, Z. Z., Zhu, J. P., Li, M., Xue, Q. Q., Zeng, Y., and Wang, Z. P. (2014b). Effects of freshwater bacterial siderophore on Microcystis and Anabaena. *Biological Control*. 78, 42-48.

Lodish, H., Berk, A., and L., Z. S. (2000). *Molecular Cell Biology. 4th edition*. New York: W. H. Freeman.

Loiselay, C., Gumpel, N. J., Girard-Bascou, J., Watson, A. T., Purton, S., Wollman, F. A., and Choquet, Y. (2008). Molecular identification and function of cis- and trans-acting determinants for *petA* transcript stability in *Chlamydomonas reinhardtii* chloroplasts. *Mol Cell Biol*. 28(17), 5529-42.

Long, J. C., Sommer, F., Allen, M. D., Lu, S. F., and Merchant, S. S. (2008). FER1 and FER2 encoding two ferritin complexes in *Chlamydomonas reinhardtii* chloroplasts are regulated by iron. *Genetics*. 179(1), 137-47.

Lopes, C. T., Franz, M., Kazi, F., Donaldson, S. L., Morris, Q., and Bader, G. D. (2010). Cytoscape Web: an interactive web-based network browser. *Bioinformatics*. 26(18), 2347-2348.

Lubián, L. M., Montero, O., Moreno-Garrido, I., Huertas, I. E., Sobrino, C., González-del Valle, M., and Parés, G. (2000). *Nannochloropsis* (Eustigmatophyceae) as source of commercially valuable pigments. *Journal of Applied Phycology*. 12(3), 249-255.

Lüttge, U., Beyschlag, W., and Murata, J. (2007). *Progress in Botany 69*. Springer Berlin Heidelberg.

Maere, S., Heymans, K., and Kuiper, M. (2005). BiNGO: a Cytoscape plugin to assess overrepresentation of gene ontology categories in biological networks. *Bioinformatics*. 21(16), 3448-3449.

Magrane, M., and Consortium, U. (2011). UniProt Knowledgebase: a hub of integrated protein data. *Database: The Journal of Biological Databases and Curation*. 2011, bar009.

Mahdavi, M. A., and Lin, Y.-H. (2007). False positive reduction in protein-protein interaction predictions using gene ontology annotations. *BMC Bioinformatics*. 8(1), 262.

Mann, M., Ong, S.-E., Grønborg, M., Steen, H., Jensen, O. N., and Pandey, A. (2002). Analysis of protein phosphorylation using mass spectrometry: deciphering the phosphoproteome. *Trends in Biotechnology*. 20(6), 261-268.

Markevičius, A., Katinas, V., Perednis, E., and Tamašauskienė, M. (2010). Trends and sustainability criteria of the production and use of liquid biofuels. *Renewable and Sustainable Energy Reviews*. 14(9), 3226-3231.

Martin, G. J. O., Hill, D. R. A., Olmstead, I. L. D., Bergamin, A., Shears, M. J., Dias, D. A., Kentish, S. E., Scales, P. J., Botté, C. Y., and Callahan, D. L. (2014). Lipid profile remodeling in response to nitrogen deprivation in the microalgae *Chlorella sp.* (Trebouxiophyceae) and *Nannochloropsis sp.* (Eustigmatophyceae). *PLOS ONE*. 9(8), e103389.

Martin, T. C., Martin, J. W., and Alison, G. S. (2006). Algae need their vitamins. *Eukaryotic Cell August*. 5(8), 1175-1183.

Mata, T. M., Martins, A. A., and Caetano, N. S. (2010). Microalgae for biodiesel production and other applications: A review. *Renewable and Sustainable Energy Reviews*. 14(1), 217-232.

Maul, J. E., Lilly, J. W., Cui, L., dePamphilis, C. W., Miller, W., Harris, E. H., and Stern, D. B. (2002). The *Chlamydomonas reinhardtii* plastid chromosome: Islands of genes in a sea of repeats. *The Plant Cell*. 14(11), 2659-2679.

Merchant, S. S., Kropat, J., Liu, B., Shaw, J., and Warakanont, J. (2012). TAG, You're it! *Chlamydomonas* as a reference organism for understanding algal triacylglycerol accumulation. *Current Opinion in Biotechnology*. 23(3), 352-363.

Michael, S. (2008). Biofuels and biomass-to-liquid fuels in the biorefinery: catalytic conversion of lignocellulosic biomass using porous materials. *Angewandte Chemie International Edition*. 47(48), 9200–9211.

Minic, Z. (2015). Proteomic Studies of the Effects of Different Stress Conditions on Central Carbon Metabolism in Microorganisms. *J Proteomics Bioinform*. 8, 080-090.

Mirón, A. S., García, M. C. C., Gómez, A. C., Camacho, F. G. a., Grima, E. M., and Chisti, Y. (2003). Shear stress tolerance and biochemical characterization of Phaeodactylum tricornutum in quasi steady-state continuous culture in outdoor photobioreactors. *Biochemical Engineering Journal*. 16(3), 287-297.

Mohammad, M., Behnam, H., Shidwash, D., and Ahmad, R. (2015). Optimization of culture media for lipid production by *Nannochloropsis oculata* for biodiesel production. *Environmental health engineering and management* 3(2), 141-17.

Moroney, J. V., and Ynalvez, R. A. (2009). *Algal Photosynthesis* Chichester: John Wiley & Sons Ltd

Morris, J. H., Apeltsin, L., Newman, A. M., Baumbach, J., Wittkop, T., Su, G., Bader, G. D., and Ferrin, T. E. (2011). clusterMaker: a multi-algorithm clustering plugin for Cytoscape. *BMC Bioinformatics*. 12, 436.

Morrissey, J., and Bowler, C. (2012). Iron utilization in marine cyanobacteria and eukaryotic algae. *Front Microbiol*. 3.

Morrissey, J., Sutak, R., Paz-Yepes, J., Tanaka, A., Moustafa, A., Veluchamy, A., Thomas, Y., Botebol, H., Bouget, F.-Y., McQuaid, Jeffrey B., Tirichine, L., Allen, Andrew E., Lesuisse, E., and Bowler, C. (2015). A Novel Protein, Ubiquitous in Marine Phytoplankton, Concentrates Iron at the Cell Surface and Facilitates Uptake. *Current Biology*. 25(3), 364-371.

Mubarak, M., Shaija, A., and Suchithra, T. V. (2015). A review on the extraction of lipid from microalgae for biodiesel production. *Algal Research*. 7, 117-123.

Mühlroth, A., Li, K., Røkke, G., Winge, P., Olsen, Y., Hohmann-Marriott, M., Vadstein, O., and Bones, A. (2013). Pathways of Lipid Metabolism in Marine Algae, Co-Expression Network, Bottlenecks and Candidate Genes for Enhanced Production of EPA and DHA in Species of Chromista. *Marine Drugs*. 11(11), 4662.

Muley, V. Y., and Ranjan, A. (2013). Evaluation of Physical and Functional Protein-Protein Interaction Prediction Methods for Detecting Biological Pathways. *PLOS ONE*. 8(1), e54325.

Muller, H. M., Kenny, E. E., and Sternberg, P. W. (2004). Textpresso: an ontology-based information retrieval and extraction system for biological literature. *PLoS Biol*. 2(11), e309.

Murata, N., and Wada, H. (1995). Acyl-lipid desaturases and their importance in the tolerance and acclimatization to cold of cyanobacteria. *Biochemical Journal*. 308(Pt 1), 1-8.

Murphy, D. J., and Leech, R. M. (1981). Photosynthesis of Lipids from CO(2) in Spinacia oleracea. *Plant Physiol*. 68(3), 762-5.

Neumara, L. S. H., Amanda, P. P., Donato, A. G. A., and Lídia Maria, P. M. (2014). Enhancement of cell growth and lipid content of a freshwater microalga

Scenedesmus sp. by optimizing nitrogen, phosphorus and vitamin concentrations for biodiesel production *atural Science*. 6.

Ng, I. S., Tan, S. I., Kao, P. H., Chang, Y. K., and Chang, J. S. (2017). Recent Developments on Genetic Engineering of Microalgae for Biofuels and Bio-Based Chemicals. *Biotechnol J*. 12(10).

Ngangkham, M., Ratha, S. K., Prasanna, R., Saxena, A. K., Dhar, D. W., Sarika, C., and Prasad, R. B. N. (2012). Biochemical modulation of growth, lipid quality and productivity in mixotrophic cultures of Chlorella sorokiniana. *SpringerPlus*. 1, 33.

Nguyen, G. T. D. T., Scaife, M. A., Helliwell, K. E., and Smith, A. G. (2016). Role of riboswitches in gene regulation and their potential for algal biotechnology. *Journal of Phycology*. 52(3), 320-328.

Nguyen, H. M., Baudet, M., Cuiné, S., Adriano, J.-M., Barthe, D., and Billon, E. (2011). Proteomic profiling of oil bodies isolated from the unicellular green microalga Chlamydomonas reinhardtii: with focus on proteins involved in lipid metabolism. *Proteomics*. 11.

Osanai, T., Park, Y. I., and Nakamura, Y. (2017). *Biotechnology of microalgae, based on molecular biology and biochemistry of eukaryotic algae and cyanobacteria*.

Paerl, R. W., Bertrand, E. M., Allen, A. E., Palenik, B., and Azam, F. (2015). Vitamin B1 ecophysiology of marine picoeukaryotic algae: Strain-specific differences and a new role for bacteria in vitamin cycling. *Limnology and Oceanography*. 60(1), 215-228.

Palanichamy, S., and Rani, V. (2004). Observation on the long term preservation and culture of the marine microlagae, *Nannochloropsis oculata*. *J mar biol Ass India*. 1(46), 98-103.

Paley, S., and Karp, P. D. (2017). Update notifications for the BioCyc collection of databases. *Database: The Journal of Biological Databases and Curation*. 2017, bax086.

Papanikolaou, N., Pavlopoulos, G., Theodosiou, T., and Iliopoulos, I. (2014). *Protein–protein interaction predictions using text mining methods*.

Pearson, W. R. (2013). An Introduction to Sequence Similarity ("Homology") Searching. *Current protocols in bioinformatics / editoral board, Andreas D Baxevanis [et al]*. 0 3, 10.1002/0471250953.bi0301s42.

Pejchal, R., and Ludwig, M. L. (2005). Cobalamin-Independent Methionine Synthase (MetE): A Face-to-Face Double Barrel That Evolved by Gene Duplication. *PLOS Biology*. 3(2), e31.

Pellegrini, M. (2012). Using phylogenetic profiles to predict functional relationships. *Methods Mol Biol*. 804, 167-77.

Peng, H., Wei, D., Chen, G., and Chen, F. (2016). Transcriptome analysis reveals global regulation in response to CO(2) supplementation in oleaginous microalga Coccomyxa subellipsoidea C-169. *Biotechnology for Biofuels*. 9, 151.

Perez-Garcia, O., Escalante, F. M. E., de-Bashan, L. E., and Bashan, Y. (2011). Heterotrophic cultures of microalgae: Metabolism and potential products. *Water Research*. 45(1), 11-36.

Perrin, D. (2012). *Buffers for pH and Metal Ion Control*. Springer Netherlands.

Pikuta, E. V., and Hoover, R. B. (2007). Microbial extremophiles at the limits of life. *Crit Rev Microbiol*. 3(33), 183-209.

Pimentel, D., and Burgess, M. (2014). Biofuel production using food. *Environment, Development and Sustainability*. 16(1), 1-3.

Pitre, S., Alamgir, M., Green, J. R., Dumontier, M., Dehne, F., and Golshani, A. (2008). Computational methods for predicting protein-protein interactions. *Adv Biochem Eng Biotechnol*. 110, 247-67.

Pizzuti, C., and Rombo, S. E. (2014). Algorithms and tools for protein–protein interaction networks clustering, with a special focus on population-based stochastic methods. *Bioinformatics*. 30(10), 1343-1352.

Podkowinski, J., and Tworak, A. (2011). Acetyl-coenzyme A carboxylase– an attractive enzyme for biotechnology. *Journal of Biotechnology, Computational Biology and Bionanotechnology*. 4(92), 321-335.

Popescu, C. E., Borza, T., Bielawski, J. P., and Lee, R. W. (2006). Evolutionary Rates and Expression Level in *Chlamydomonas*. *Genetics*. 172(3), 1567-1576.

Powell, N., Shilton, A., Chisti, Y., and Pratt, S. (2009). Towards a luxury uptake process via microalgae – Defining the polyphosphate dynamics. *Water Research*. 43(17), 4207-4213.

Prafulla, D. P., Veera, G. G., and Shuguang, D. (2009). Biodiesel production from *jatropha curcas*, waste cooking, and *camelina sativa* oils. *Ind Eng Chem Res*. (48), 10850–10856.

Provasoli, L., and Carlucci, A. F. (1974). *Vitamins and growth regulators*. Oxford, United Kingdom: Blackwell Scientific Publications.

Qin, J. G. (2010). Lipid-Containing Secondary Metabolites from Algae. In Timmis, K. N. (Ed.) *Handbook of Hydrocarbon and Lipid Microbiology* (pp. 3021-3030). Berlin, Heidelberg: Springer Berlin Heidelberg.

Qiu, R., Gao, S., Lopez, P. A., and Ogden, K. L. (2017). Effects of pH on cell growth, lipid production and CO_2 addition of microalgae *Chlorella sorokiniana*. *Algal Research*. 28(Supplement C), 192-199.

Radakovits, R., Jinkerson, R. E., Darzins, A., and Posewitz, M. C. (2010). Genetic engineering of algae for enhanced biofuel production. *Eukaryot Cell*. 9.

Raman, K. (2010). Construction and analysis of protein–protein interaction networks. *Automated Experimentation*. 2(1), 2.

Ramos, M. J., Fernández, C. M., Casas, A., Rodríguez, L., and Pérez, Á. (2009). Influence of fatty acid composition of raw materials on biodiesel properties. *Bioresource Technology*. 100(1), 261-268.

Ranganathan, S. V., Narasimhan, S. L., and Muthukumar, K. (2008). An overview of enzymatic production of biodiesel. *Bioresource Technology*. 99(10), 3975-3981.

Ranjith Kumar, R., Hanumantha Rao, P., and Arumugam, M. (2015). Lipid extraction methods from microalgae: a comprehensive review. *frontiers in energy research*. 2.

Rasoul-Amini, S., Montazeri-Najafabady, N., Mobasher, M. A., Hoseini-Alhashemi, S., and Ghasemi, Y. (2011). *Chlorella* sp.: A new strain with highly saturated fatty acids for biodiesel production in bubble-column photobioreactor. *Appl Energ*. 88(10), 3354-3356.

Razzak, S. A., Hossain, M. M., Lucky, R. A., Bassi, A. S., and de Lasa, H. (2013). Integrated CO2 capture, wastewater treatment and biofuel production by microalgae culturing—A review. *Renewable and Sustainable Energy Reviews*. 27, 622-653.

Richmond, A., and Hu, Q. (2013). *Handbook of Microalgal Culture: Applied Phycology and Biotechnology*. Wiley.

Richmond, A., and Richmond, A. (2004). *Handbook of microalgal mass, culture, biotechnology and applied phycology*.

Rupprecht, J. (2009). From systems biology to fuel—Chlamydomonas reinhardtii as a model for a systems biology approach to improve biohydrogen production. *Journal of Biotechnology*. 142(1), 10-20.

Sabetian, S., and Shamsir, M. S. (2015). Identification of putative drug targets for human sperm-egg interaction defect using protein network approach. *BMC Systems Biology*. 9, 37.

Sabetian, S., and Shamsir, M. S. (2016). Systematic Analysis of Protein Interaction Network Associated with Azoospermia. *International Journal of Molecular Sciences*. 17(11), 1857.

Saito, R., Smoot, M. E., Ono, K., Ruscheinski, J., Wang, P.-L., Lotia, S., Pico, A. R., Bader, G. D., and Ideker, T. (2012). A travel guide to Cytoscape plugins. *Nature methods*. 9(11), 1069-1076.

Saladini, F., Patrizi, N., Pulselli, F. M., Marchettini, N., and Bastianoni, S. (2016). Guidelines for emergy evaluation of first, second and third generation biofuels. *Renewable and Sustainable Energy Reviews*. 66, 221-227.

Samira, C., Mahmah, B., Chetehouna, K., and Mignolet, E. (2010). *Biodiesel production using Chlorella sorokiniana a green microalga*.

Sandmann, G. (1985). Consequences of iron deficiency on photosynthetic and respiratory electron transport in blue-green algae. *Photosynthesis Research*. 6(3), 261-271.

Santos, A. M., Janssen, M., Lamers, P. P., Evers, W. A. C., and Wijffels, R. H. (2012). Growth of oil accumulating microalga *Neochloris oleoabundans* under alkaline–saline conditions. *Bioresource Technology*. 104, 593-599.

Sañudo-Wilhelmy, S. A., Cutter, L. S., Durazo, R., Smail, E. A., Gómez-Consarnau, L., Webb, E. A., Prokopenko, M. G., Berelson, W. M., and Karl, D. M. (2012). Multiple B-vitamin depletion in large areas of the coastal ocean. *Proceedings of the National Academy of Sciences*. 109(35), 14041-14045.

Sarmidi, A. (2009). Review on biofuel oil and gas production processes from microalgae. *Energy Conversion and Management*. 50(7), 1834-1840.

Sasireka, G., and Muthuvelayudham, R. (2015). Effect of salinity and iron stressed on growth and lipid accumulation in *Skeletonema costatum* for biodiesel production. *Res J Chem Sci*. 5(5), 69-72.

Sato, N., Hagio, M., Wada, H., and Tsuzuki, M. (2000). Requirement of phosphatidylglycerol for photosynthetic function in thylakoid membranes. *Proceedings of the National Academy of Sciences*. 97(19), 10655-10660.

Sayre, R. (2010). Microalgae: The Potential for Carbon Capture. *BioScience*. 60(9), 722-727.

Schenk, P. M., Thomas-Hall, S. R., Stephens, E., Marx, U. C., Mussgnug, J. H., Posten, C., Kruse, O., and Hankamer, B. (2008). Second Generation Biofuels: High-Efficiency Microalgae for Biodiesel Production. *BioEnergy Research*. 1(1), 20-43.

Schwarz, C., Elles, I., Kortmann, J., Piotrowski, M., and Nickelsen, J. (2007). Synthesis of the D2 protein of photosystem II in *Chlamydomonas* is controlled by a high molecular mass complex containing the RNA stabilization factor nac2 and the translational activator RBP40. *The Plant Cell*. 19(11), 3627-3639.

Scott-Boyer, M. P., Lacroix, S., Scotti, M., Morine, M. J., Kaput, J., and Priami, C. (2016). A network analysis of cofactor-protein interactions for analyzing associations between human nutrition and diseases. *Scientific Reports*. 6, 19633.

Scott, S. A., Davey, M. P., Dennis, J. S., Horst, I., Howe, C. J., Lea-Smith, D. J., and Smith, A. G. (2010). Biodiesel from algae: challenges and prospects. *Curr Opin Biotechnol*. 21.

Scranton, M. A., Ostrand, J. T., Fields, F. J., and Mayfield, S. P. (2015). Chlamydomonas as a model for biofuels and bio-products production. *Plant J*. 82(3), 523-31.

Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., Amin, N., Schwikowski, B., and Ideker, T. (2003). Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res*. 13.

Sharif., H., Aishah., S., Amru, N. B., Partha, C., and Mohd, N. (2008). Biodiesel fuel production from algae as renewable energy. *American Journal of Biochemistry and Biotechnology*. 4(3), 250-254.

Sharifah, E. N., and Eguchi, M. (2011). The phytoplankton *Nannochloropsis oculata* enhances the ability of *Roseobacter clade* bacteria to inhibit the growth of fish pathogen *Vibrio anguillarum*. *PLoS ONE*. 6(10), e26756.

Shen, J., Zhang, J., Luo, X., Zhu, W., Yu, K., Chen, K., Li, Y., and Jiang, H. (2007). Predicting protein-protein interactions based only on sequences information. *Proc Natl Acad Sci U S A*. 104(11), 4337-41.

Shoemaker, B. A., and Panchenko, A. R. (2007). Deciphering protein-protein interactions. Part I. Experimental techniques and databases. *PLoS Comput Biol*. 3.

Siaut, M., Cuiné, S., Cagnon, C., Fessler, B., Nguyen, M., and Carrier, P. (2011). Oil accumulation in the model green alga Chlamydomonas reinhardtii: characterization, variability between common laboratory strains and relationship with starch reserves. *BMC Biotechnol*. 11.

Simionato, D., Block, M. A., La Rocca, N., Jouhet, J., Marechal, E., Finazzi, G., and Morosinotto, T. (2013). The response of Nannochloropsis gaditana to nitrogen starvation includes de novo biosynthesis of triacylglycerols, a decrease of chloroplast galactolipids, and reorganization of the photosynthetic apparatus. *Eukaryot Cell*. 12(5), 665-76.

Slade, R., and Bauen, A. (2013). Micro-algae cultivation for biofuels: Cost, energy balance, environmental impacts and future prospects. *Biomass and Bioenergy*. 53, 29-38.

Spalding, M. H. (2009). The CO2-concentrating mechanism and carbon assimilation. In Stern, D. B. (Ed.) *The Chlamydomonas Sourcebook* (pp. Oxford: Acadamic Press/Elsevier.

Spolaore, P., Joannis-Cassan, C., Duran, E., and Isambert, A. (2006). Optimization of *Nannochloropsis oculata* growth using the response surface method. *J Chem Technol Biotechnol*. 18(6), 1049-1056.

Stanke, M., Schöffmann, O., Morgenstern, B., and Waack, S. (2006). Gene prediction in eukaryotes with a generalized hidden Markov model that uses hints from external sources. *BMC Bioinformatics*. 7, 62-62.

Stansell, G. R., Gray, V. M., and Sym, S. D. (2012). Microalgal fatty acid composition: implications for biodiesel quality. *Journal of Applied Phycology*. 24(4), 791-801.

Stec, B. (2012). Structural mechanism of RuBisCO activation by carbamylation of the active site lysine. *Proceedings of the National Academy of Sciences of the United States of America*. 109(46), 18785-18790.

Steffii, F., Brendan, M., and Erin, N. (2003). Nitrate and phosphate levels positively affect the growth of algae species found in Perry Pond. *Grinnell College*. 4, 21-24.

Stelzl, U., Worm, U., Lalowski, M., Haenig, C., Brembeck, F. H., Goehler, H., Stroedicke, M., Zenkner, M., Schoenherr, A., Koeppen, S., Timm, J., Mintzlaff, S., Abraham, C., Bock, N., Kietzmann, S., Goedde, A., Toksöz, E., Droege, A., Krobitsch, S., Korn, B., Birchmeier, W., Lehrach, H., and Wanker, E. E. (2005). A Human Protein-Protein Interaction Network: A Resource for Annotating the Proteome. *Cell*. 122(6), 957-968.

Stephens, E., Ross, I. L., Mussgnug, J. H., Wagner, L. D., Borowitzka, M. A., and Posten, C. (2010). Future prospects of microalgal biofuel production systems. *Trends Plant Sci*. 15.

Stern, D. (2009). *The Chlamydomonas sourcebook: organellar and metabolic processes*. Elsevier Science.

Streit, W. R., and Entcheva, P. (2003). Biotin in microbes, the genes involved in its biosynthesis, its biochemical role and perspectives for biotechnological production. *Appl Microbiol Biotechnol*. 61(1), 21-31.

Su, C.-H., Chien, L.-J., Gomes, J., Lin, Y.-S., Yu, Y.-K., Liou, J.-S., and Syu, R.-J. (2011). Factors affecting lipid accumulation by Nannochloropsis oculata in a two-stage cultivation process. *Journal of Applied Phycology*. 23(5), 903-908.

Summerfield, T. C., Crawford, T. S., Young, R. D., Chua, J. P., Macdonald, R. L., Sherman, L. A., and Eaton-Rye, J. J. (2013). Environmental pH affects photoautotrophic growth of *Synechocystis* sp. PCC 6803 strains carrying mutations in the lumenal proteins of PSII. *Plant Cell Physiol*. 54(6), 859-74.

Summerfield, T. C., and Sherman, L. A. (2008). Global Transcriptional Response of the Alkali-Tolerant *Cyanobacterium Synechocystis* sp. Strain PCC 6803 to a pH 10 Environment. *Applied and Environmental Microbiology*. 74(17), 5276-5284.

Suzuki, T., Tada, O., Makimura, M., Tohri, A., Ohta, H., Yamamoto, Y., and Enami, I. (2004). Isolation and characterization of oxygen-evolving photosystem II

complexes retaining the PsbO, P and Q proteins from *Euglena gracilis*. *Plant and Cell Physiology*. 45(9), 1168-1175.

Szilagyi, A., Grimm, V., Arakaki, A. K., and Skolnick, J. (2005). Prediction of physical protein-protein interactions. *Phys Biol*. 2(2), S1-16.

Szklarczyk, D., Franceschini, A., Kuhn, M., Simonovic, M., Roth, A., Minguez, P., Doerks, T., Stark, M., Muller, J., Bork, P., Jensen, L. J., and von Mering, C. (2011). The STRING database in 2011: functional interaction networks of proteins, globally integrated and scored. *Nucleic Acids Research*. 39(Database issue), D561-D568.

Szklarczyk, D., Morris, J. H., Cook, H., Kuhn, M., Wyder, S., Simonovic, M., Santos, A., Doncheva, N. T., Roth, A., Bork, P., Jensen, L. J., and von Mering, C. (2017). The STRING database in 2017: quality-controlled protein–protein association networks, made broadly accessible. *Nucleic Acids Research*. 45(Database issue), D362-D368.

Takagi, M., Watanabe, K., Yamaberi, K., and Yoshida, T. (2000). Limited feeding of potassium nitrate for intracellular lipid and triglyceride accumulation of *Nannochloris* sp. UTEX LB1999. *Applied Microbiology and Biotechnology*. 54(1), 112-117.

Talib, O. (2015). *SPSS: Analisis Data Kuantitatif Untuk Penyelidik Muda*. MPWS Rich Publication Sdn. Bhd.

Tan, K. W. M., and Lee, Y. K. (2016). The dilemma for lipid productivity in green microalgae: importance of substrate provision in improving oil yield without sacrificing growth. *Biotechnology for Biofuels*. 9(1), 255.

Tang, Y. Z., Koch, F., and Gobler, C. J. (2010). Most harmful algal bloom species are vitamin B1 and B12 auxotrophs. *Proceedings of the National Academy of Sciences*. 107(48), 20756-20761.

Taniar, D. (2006). *Research and Trends in Data Mining Technologies and Applications*. Idea Group Pub.

Taraldsvik, M., and Myklestad, S. M. (2000). The effect of pH on growth rate, biochemical composition and extracellular carbohydrate production of the marine diatom *Skeletonema costatum*. *Eur J Phycol*. 35(2), 189-194.

Tardif, M., Atteia, A., Specht, M., Cogne, G., Rolland, N., Brugière, S., Hippler, M., Ferro, M., Bruley, C., Peltier, G., Vallon, O., and Cournac, L. (2012).

PredAlgo: A New Subcellular Localization Prediction Tool Dedicated to Green Algae. *Molecular Biology and Evolution*. 29(12), 3625-3639.

Tasić, M. B., Pinto, L. F. R., Klein, B. C., Veljković, V. B., and Filho, R. M. (2016). Botryococcus braunii for biodiesel production. *Renewable and Sustainable Energy Reviews*. 64, 260-270.

Teo, C. L., Jamaluddin, H., Zain, N. A. M., and Idris, A. (2014). Biodiesel production via lipase catalysed transesterification of microalgae lipids from *Tetraselmis* sp. *Renew Energ*. 68, 1-5.

Terzulli, A., and Kosman, D. J. (2010). Analysis of the High-Affinity Iron Uptake System at the Chlamydomonas reinhardtii Plasma Membrane. *Eukaryotic Cell*. 9(5), 815-826.

Tong, L. (2013). Structure and function of biotin-dependent carboxylases. *Cellular and molecular life sciences : CMLS*. 70(5), 863-891.

Tonon, T., Harvey, D., Larson, T. R., and Graham, I. A. (2002). Long chain polyunsaturated fatty acid production and partitioning to triacylglycerols in four microalgae. *Phytochemistry*. 61(1), 15-24.

Touloupakis, E., Cicchi, B., Benavides, A. M. S., and Torzillo, G. (2016). Effect of high pH on growth of *Synechocystis* sp. PCC 6803 cultures and their contamination by golden algae (*Poterioochromonas* sp.). *Applied Microbiology and Biotechnology*. 100, 1333-1341.

Trisilowati, and Mallet, D. G. (2012). In silico experimental modeling of cancer treatment. *ISRN oncology*. 2012, 828701-828701.

Turanalp, M. E., and Can, T. (2008). Discovering functional interaction patterns in protein-protein interaction networks. *BMC Bioinformatics*. 9, 276-276.

Urzica, E. I., Vieler, A., Hong-Hermesdorf, A., Page, M. D., Casero, D., Gallaher, S. D., Kropat, J., Pellegrini, M., Benning, C., and Merchant, S. S. (2013). Remodeling of membrane lipids in iron-starved Chlamydomonas. *J Biol Chem*. 288.

Vaistij, F. E., Goldschmidt-Clermont, M., Wostrikoff, K., and Rochaix, J. D. (2000). Stability determinants in the chloroplast psbB/T/H mRNAs of *Chlamydomonas reinhardtii*. *Plant J*. 21(5), 469-82.

Veillette, M., Chamoumi, M., Nikiema, J., Faucheux, N., and Michèle Heitz, M. (2012). *Production of Biodiesel from Microalgae*. Croatia: Adv. Chem. Eng.

von Mering, C., Jensen, L. J., Snel, B., Hooper, S. D., Krupp, M., Foglierini, M., Jouffre, N., Huynen, M. A., and Bork, P. (2005). STRING: known and predicted protein-protein associations, integrated and transferred across organisms. *Nucleic Acids Res*. 33.

von Mering, C., Krause, R., Snel, B., Cornell, M., Oliver, S. G., Fields, S., and Bork, P. (2002). Comparative assessment of large-scale data sets of protein-protein interactions. *Nature*. 417.

Waldrop, G. L., Holden, H. M., and Maurice, M. S. (2012). The enzymes of biotin dependent CO_2 metabolism: What structures reveal about their reaction mechanisms. *Protein Science*. 21(11), 1597-1619.

Wan, M., Jin, X., Xia, J., Rosenberg, J. N., Yu, G., Nie, Z., Oyler, G. A., and Betenbaugh, M. J. (2014). The effect of iron on growth, lipid accumulation, and gene expression profile of the freshwater microalga Chlorella sorokiniana. *Applied Microbiology and Biotechnology*. 98(22), 9473-9481.

Wang, B., and Lan, C. Q. 2010. Microalgae for biofuel production and CO_2 sequesstration. New York: Nova Science Publisher, Inc.

Wang, B., Li, Y., Wu, N., and Lan, C. Q. (2008). CO2 bio-mitigation using microalgae. *Applied Microbiology and Biotechnology*. 79(5), 707-718.

Wang, D., Ning, K., Li, J., Hu, J., Han, D., Wang, H., Zeng, X., Jing, X., Zhou, Q., Su, X., Chang, X., Wang, A., Wang, W., Jia, J., Wei, L., Xin, Y., Qiao, Y., Huang, R., Chen, J., Han, B., Yoon, K., Hill, R. T., Zohar, Y., Chen, F., Hu, Q., and Xu, J. (2014). Nannochloropsis Genomes Reveal Evolution of Microalgal Oleaginous Traits. *PLOS Genetics*. 10(1), e1004094.

Wang, F., Johnson, X., Cavaiuolo, M., Bohne, A.-V., Nickelsen, J., and Vallon, O. (2015a). Two *Chlamydomonas* OPR proteins stabilize chloroplast mRNAs encoding small subunits of photosystem II and cytochrome b6f. *The Plant Journal*. 82(5), 861-873.

Wang, H.-T., Meng, Y.-Y., Cao, X.-P., Ai, J.-N., Zhou, J.-N., Xue, S., and Wang, W.-l. (2015b). Coordinated response of photosynthesis, carbon assimilation, and triacylglycerol accumulation to nitrogen starvation in the marine microalgae Isochrysis zhangjiangensis (Haptophyta). *Bioresource Technology*. 177(Supplement C), 282-288.

Wang, Y., Duanmu, D., and Spalding, M. H. (2011). Carbon dioxide concentrating mechanism in *Chlamydomonas reinhardtii*: inorganic carbon transport and CO_2 recapture. *Photosynthesis Research*. 109(1), 115-122.

Wang, Z. T., Ullrich, N., Joo, S., Waffenschmidt, S., and Goodenough, U. (2009). Algal Lipid Bodies: Stress Induction, Purification, and Biochemical Characterization in Wild-Type and Starchless Chlamydomonas reinhardtii. *Eukaryotic Cell*. 8(12), 1856-1868.

Wiley, B. (2013). *Handbook of microalgal culture*. (2). United Kingdom: John Wiley & Sons, Ltd.

Wilhelm, C., and Jakob, T. (2011). From photons to biomass and biofuels: evaluation of different strategies for the improvement of algal biotechnology based on comparative energy balances. *Applied Microbiology and Biotechnology*. 92(5), 909-919.

Wu, G., Feng, X., and Stein, L. (2010). A human functional protein interaction network and its application to cancer data analysis. *Genome Biology*. 11(5), R53-R53.

Wu, S., Huang, A., Zhang, B., Huan, L., Zhao, P., and Lin, A. (2015). Enzyme activity highlights the importance of the oxidative pentose phosphate pathway in lipid accumulation and growth of Phaeodactylum tricornutum under CO2 concentration. *Biotechnol Biofuels*. 8.

Wu, X., and Qi, X. (2010). Genes encoding hub and bottleneck enzymes of the Arabidopsis metabolic network preferentially retain homeologs through whole genome duplication. *BMC Evolutionary Biology*. 10, 145-145.

Wurch, L. L., Bertrand, E. M., Saito, M. A., Van Mooy, B. A. S., and Dyhrman, S. T. (2011). Proteome Changes Driven by Phosphorus Deficiency and Recovery in the Brown Tide-Forming Alga Aureococcus anophagefferens. *PLOS ONE*. 6(12), e28949.

Xie, B., Bishop, S., Stessman, D., Wright, D., Spalding, M. H., and Halverson, L. J. (2013). *Chlamydomonas reinhardtii* thermal tolerance enhancement mediated by a mutualistic interaction with vitamin B(12)-producing bacteria. *The ISME Journal*. 7(8), 1544-1555.

Xin, L., Hong-ying, H., Ke, G., and Ying-xue, S. (2010). Effects of different nitrogen and phosphorus concentrations on the growth, nutrient uptake, and lipid

accumulation of a freshwater microalga Scenedesmus sp. *Bioresource Technology*. 101(14), 5494-5500.

Xing, S., Wallmeroth, N., Berendzen, K. W., and Grefen, C. (2016). Techniques for the Analysis of Protein-Protein Interactions in Vivo. *Plant Physiology*. 171(2), 727-758.

Xu, B., Liu, Y., Lin, C., Dong, J., Liu, X., and He, Z. (2018). Reconstruction of the protein-protein interaction network for protein complexes identification by walking on the protein pair fingerprints similarity network. *Frontiers in Genetics*. 9, 272.

Xu, J., Zheng, Z., and Zou, J. (2009). A membrane-bound glycerol-3-phosphate acyltransferase from Thalassiosira pseudonana regulates acyl composition of glycerolipidsThis paper is one of a selection of papers published in a Special Issue from the National Research Council of Canada – Plant Biotechnology Institute. *Botany*. 87(6), 544-551.

Xu, Z., Zou, D., and Gao, K. (2010). Effects of elevated CO_2 and phosphorus supply on growth, photosynthesis and nutrient uptake in the marine macroalga Gracilaria lemaneiformis. *Botanica Marina*. (53), 123–129.

Yagisawa, F., Nishida, K., Yoshida, M., Ohnuma, M., Shimada, T., Fujiwara, T., Yoshida, Y., Misumi, O., Kuroiwa, H., and Kuroiwa, T. (2009). Identification of novel proteins in isolated polyphosphate vacuoles in the primitive red alga *Cyanidioschyzon merolae*. *The Plant Journal*. 60(5), 882-893.

Yazawa, H., Iwahashi, H., Kamisaka, Y., Kimura, K., and Uemura, H. (2009). Production of polyunsaturated fatty acids in yeast Saccharomyces cerevisiae and its relation to alkaline pH tolerance. *Yeast*. 26(3), 167-84.

Ye, P., Peyser, B. D., Spencer, F. A., and Bader, J. S. (2005). Commensurate distances and similar motifs in genetic congruence and protein interaction networks in yeast. *BMC Bioinformatics*. 6(1), 270.

Yeh, C.-Y., Yeh, H.-Y., Arias, C. R., and Soo, V.-W. (2012). Pathway detection from protein interaction networks and gene expression data using color-coding methods and A∗ search algorithms. *The Scientific World Journal*. 2012, 315797.

Yellaboina, S., Goyal, K., and Mande, S. C. (2007). Inferring genome-wide functional linkages in *E. coli* by combining improved genome context methods:

comparison with high-throughput experimental data. *Genome Research*. 17(4), 527-535.

Yokomizo, T., and Murakami, M. (2015). *Bioactive Lipid Mediators: Current Reviews and Protocols*. Springer Japan.

Yoon, J. S., and Jung, W.-H. (2011). A GPU-accelerated bioinformatics application for large-scale protein interaction networks. *APBC poster presentation*.

Yu, H., Kim, P. M., Sprecher, E., Trifonov, V., and Gerstein, M. (2007). The Importance of Bottlenecks in Protein Networks: Correlation with Gene Essentiality and Expression Dynamics. *PLoS Computational Biology*. 3(4), e59.

Zahiri, J., Bozorgmehr, J. H., and Masoudi-Nejad, A. (2013). Computational prediction of protein–protein interaction networks: algo-rithms and resources. *Current Genomics*. 14(6), 397-414.

Zhang, H. Y., Zeng, R. S., Chen, D. Y., and Liu, J. A. (2016). A pivotal role of vacuolar H(+)-ATPase in regulation of lipid production in *Phaeodactylum tricornutum*. *Scientific Reports*. 6, 31319.

Zhang, Y., Dubé, M. A., McLean, D. D., and Kates, M. (2003). Biodiesel production from waste cooking oil: 1. Process design and technological assessment. *Bioresource Technology*. 89(1), 1-16.

Zheng, H. Q., Chiang-Hsieh, Y. F., Chien, C. H., Hsu, B. K., Liu, T. L., Chen, C. N., and Chang, W. C. (2014). AlgaePath: comprehensive analysis of metabolic pathways using transcript abundance data from next-generation sequencing in green algae. *BMC Genomics*. 15, 196.

Zhou, C., Teng, W. J., Zhuang, J., Liu, H. L., Tang, S. F., Cao, X. J., Qin, B. N., Wang, C. C., and Sun, C. G. (2015). Analysis of the gene-protein interaction network in glioma. *Genet Mol Res*. 14(4), 14196-206.

Zouni, A., Witt, H.-T., Kern, J., Fromme, P., Krauss, N., Saenger, W., and Orth, P. (2001). Crystal structure of photosystem II from *Synechococcus elongatus* at 3.8 Å resolution. *Nature*. 409, 739.

Zybailov, B. L., Byrd, A. K., Glazko, G. V., Rahmatallah, Y., and Raney, K. D. (2016). Protein-Protein Interaction Analysis for Functional Characterization of Helicases. *Methods (San Diego, Calif)*. 108, 56-64.