ISSN 0000-0000
9 770000 000003

Quest ©

ज्ञानेन शीलम्

Vol. 5 No. 1

RIBAS

March- 2017

Quest

Editorial

Editorial Office
Quest, ARIBAS,
New Vallabh Vidyanagar,
Vitthal Udyognagar - 388121,
Dist- Anand, Gujarat, India.
Phone: +91-2692-229189, 231894
Fax: +91-2692-229189
Email: editor@aribas.edu.in
Website: www.aribas.edu.in

Published By
Director ARIBAS,
New Vallabh Vidyanagar,
Vitthal Udyognagar - 388121,
Dist- Anand, Gujarat, India.
Phone: +91-2692-229189, 231894
Fax: +91-2692-229189
Email: head@aribas.edu.in

Index

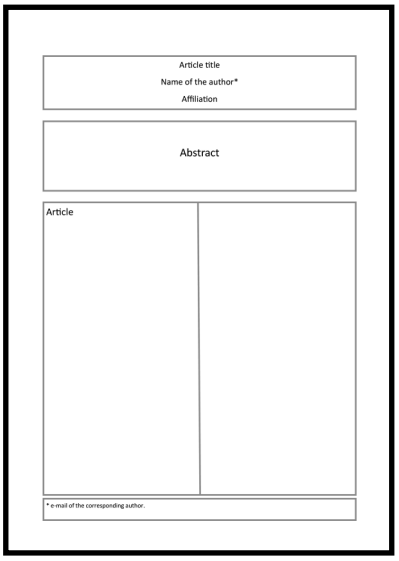
NEWS AND VIEWS:-

REVIEW ARTICLE:-

Notice to Authors

Manuscripts submitted to Quest should adhere to below mentioned criteria.
Research News: About 400 words (1 page)
Research Article: About 2000 words (4 pages)

Common for all: -
Font: Calibri
Font Size: 14
Columns: 2
Line Spacing: 1
Margin: Narrow
References: 1) In text citing, S No, Superscript.
2) Author's name (s), *Journal name*, **Volume No**, Page No**,** (year).
3) Maximum number of references should not exceed than 25.



Common antibiotic azithromycin effectively kills many multidrug-resistant bacteria

Contrary to current medical dogma, researchers at University of California, San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences report that the common antibiotic azithromycin kills many multidrug-resistant bacteria very effectively — when tested under conditions that closely resemble the human body and its natural antimicrobial factors.

Azithromycin is the most often prescribed antibiotic in the United States, where short courses can cure common bacterial infections such as strep throat and sinusitis. But azithromycin, also sold commercially as Zithromax Z-Pak, is never given to patients with some of the most nefarious multidrug-resistant bacterial infections. That's because years of testing in standard laboratory media — the nutrient broth that helps bacteria grow — concluded that azithromycin doesn't kill these types of bacteria.

The bacteria at the center of this study are Gram-negative rods, so-called due to their cell wall structure (they appear "negative" in a classic typing test known as the Gram stain) and their shape. The team studied extremely antibiotic-resistant strains of three medically important Gram-negative rods: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*. These opportunistic pathogens rarely infect healthy people but instead strike debilitated patients in hospitals, such as those with weakened immune systems, or following trauma or surgery, sometimes with deadly consequences. The Centers for Disease Control and World Health Organization have warned that resistance is rapidly spreading in these species, and no new antibiotic candidates are on the horizon.
In this study, team found that simply growing these Gram-negative rod bacteria in mammalian tissue culture media — the same stuff used to sustain human cells in the lab — instead of standard bacteriologic media made a huge difference in their sensitivity to azithromycin. Even more striking, the drug-resistant superbugs were completely wiped out when azithromycin was paired with the antibiotic colistin or with antimicrobial peptides produced naturally by the human body during infection.

To test these promising laboratory results in a live infection system, they moved the experiment into a mouse model of multidrug-resistant *A. baumannii*pneumonia. They treated the mice with a single injected dose of azithromycin at a concentration that mimics the amount typically given by IV to human patients. Twenty-four hours after infection, azithromycin-treated mice had 99 percent fewer bacteria in their lungs than untreated mice. Similarly, in mouse models of multidrug-resistant *P. aeruginosa* and *K. pneumoniae* infections, a single dose of azithromycin reduced bacterial counts by more than 10-fold.

Azithromycin interfere with the protein synthesis and prevents bacteria from growing. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA. So by considering it as a lead molecule we can do various derivatives of it and design medicines

for other multi drug resistance diseases caused due to bacteria.

Source:
UC San Diego Health System
Published on June 11, 2015

-Contributed by Ravina Sewani, M.Sc IGIBT Sem-VII

Organ-on-a-chip could replace use of animals to test drugs for safety and efficacy

When University of California, Berkeley, bioengineers say they are holding their hearts in the palms of their hands, they are not talking about emotional vulnerability. Instead, the research team led by bioengineering professor Kevin Healy is presenting a network of pulsating cardiac muscle cells housed in an inch-long silicone device that effectively models human heart tissue, and they have demonstrated the viability of this system as a drug-screening tool by testing it with cardiovascular medications.

This organ-on-a-chip, represents a major step forward in the development of accurate, faster methods of testing for drug toxicity. The project is funded through the Tissue Chip for Drug Screening Initiative, an interagency collaboration launched by the National Institutes of Health to develop 3-D human tissue chips that model the structure and function of human organs.

The study authors noted a high failure rate associated with the use of nonhuman animal models to predict human reactions to new drugs. Much of this is due to fundamental differences in biology between species, the researchers explained. For instance, the ion channels through which heart cells conduct electrical currents can vary in both number and type between humans and other animals. The heart cells were derived from human-induced pluripotent stem cells, the adult stem cells that can be coaxed to become many different types of tissue.

The researchers designed their cardiac microphysiological system, or heart-on-a-chip, so that its 3-D structure would be comparable to the geometry and spacing of connective tissue fiber in a human heart. They added the differentiated human heart cells into the loading area, a process that Healy likened to passengers boarding a subway train at rush hour. The system's confined geometry helps align the cells in multiple layers and in a single direction.

Microfluidic channels on either side of the cell area serve as models for blood vessels, mimicking the exchange by diffusion of nutrients and drugs with human tissue. In the future, this setup could also allow researchers to monitor the removal of metabolic waste products from the cells.

This system is not a simple cell culture where tissue is being bathed in a static bath of liquid, instead it is dynamic; it replicates how tissue in our bodies actually gets exposed to nutrients and drugs

Within 24 hours after the heart cells were loaded into the chamber, they began beating

on their own at a normal physiological rate of 55 to 80 beats per minute.

The researchers put the system to the test by monitoring the reaction of the heart cells to four well-known cardiovascular drugs: isoproterenol, E-4031, verapamil and metoprolol. They used changes in the heart tissue's beat rate to gauge the response to the compounds. The baseline beat rate for the heart tissue consistently fell within 55 to 80 beats per minute, a range considered normal for adult humans. They found that the responses after exposure to the drugs were predictable. For example, after half an hour of exposure to isoproterenol, a drug used to treat bradycardia (slow heart rate), the beat rate of the heart tissue increased from 55 to 124 beats per minute.

The researchers noted that their heart-on-a-chip could be adapted to model human genetic diseases or to screen for an individual's reaction to drugs. They are also studying whether the system could be used to model multi-organ interactions. A standard tissue culture plate could potentially feature hundreds of micro physiological .

The engineered heart tissue remained viable and functional over multiple weeks. Given that time, it could be used to test various drugs, Healy said.

This is an incredible chip containing heart tissues on it. This can lead to minimize the tenure of different clinical trial phases of a drug. Also lowers down the ethical issues of testing drugs on humans. We can also try to synthesize a whole organ based on this mechanism. This can be a bench mark of researches in synthesizing organs in-vitro and can be transplant in practice.

Source

University of California - Berkele

-Contributed by , Shirley Dixit,
M.Sc IGMBT Sem-VII

Bioactive Compounds from Seaweeds

Mukund Chandra Thakur [8]

Ashok & Rita Patel Institute of Integrated Study & Research in Biotechnology and Allied Sci-ences (ARIBAS), New Vallabh Vidyanagar 388121, Anand, Gujarat, India

Abstract: Seaweeds are the most diversified macroalgae present in marine water. They are most promising source of biologically active compounds which shows a broad spectrum of biotechnological interest. These seaweeds are eukaryotic in nature thalloid structure and may range from few to around several centimetres in height. Seaweeds are found from splash zone to subtidal zone (deep into the sea upto several metres). They are classified according to the pigments present in them in three main types Chlorophyta (green algae), Pheophyta (brown algae) and Rhodophyta (red algae). The main pigments present in the seaweeds are carotene, chlorophylls, lutein, siphonoxanthin and siphonein, β-carotene, fucoxanthin, r-phycocyanin, allophycocyanin, c-phycoerythrin etc. Seaweeds have been used in many purposes such as food, medicines, herbs, etc. Seaweeds are rich in many chemical compounds such as agar-agar, carrageenan, alginates etc. Seaweed extracts are important component of mast stimulated products in market and are known to conatin polysaccharides, minerals and certain vitamins. Bioactive compounds found in them are known to have anti-bacterial, antifungal and antiviral properties.

Introduction

Seaweeds are the most diversified macroalgae present in marine water. They are photosynthetic, multicellular, non-vascular and eukaryotic in nature. The size of the thallus may range from few millimetres to around 60 cm in height[1] and are attached to the hard surface in shallow water. Seaweeds are found deep into the sea upto several 40-60 metres and are bound to solid substrates such as rock, dead corals, pebbles, shells. Seaweeds are categorized into three main types Chlorophyceae (green algae), Pheophyceae (brown algae), and Rhodophyceae (red algae)[2]. They are classified according to the pigments present in them. Green seaweeds contain α-, β-, and γ- carotene, chlorophylls a and b, lutein, siphonoxanthin and siphonein. Chlorophylls a, c1, c2, β-carotene and fucoxanthin are responsible for pigmentation in brown seaweeds. Pigments found in red seaweeds are Chlorophyll a, r-phycocyanin, allophycocyanin, c-phycoerythrin, α- and β-carotene[3]. Seaweeds have been used in many purposes such as food, medicines, herbs, etc. Seaweeds produce many chemical compounds such as agar-agar, carrageenan, alginates etc. Seaweed extracts are important component of mast stimulated products in market and are known to conatin polysaccharides, minerals and certain vitamins[4]. Bioactive compounds found in

* *Corresponding Author: mukundthakur@aribas.edu.in*

them are known to have anti-bacterial, anti-fungal and antiviral properties[5].

Polysaccharides: Marine algae contain large amount of polysaccharides that are linked together by linked together by glycosidic bonds. They are used as stabilisers, thickeners, emulsifiers, food, feed, beverages, etc. in many industrial products[6]. Seaweeds contain upto 76 % (dry weight) polysaccharides. *Ascophyllum, Porphyra* and *Palmaria* contain high amount of polysaccharides. *Ulva sp.* also contains high amount upto 65% dry weight. Seaweeds are low in calories, although their lipid content is low and carbohydrate content is high. These carbohydrates cannot be utilised by humans[7]. Cellulose and hemicellulose are present in cell wall polysaccharides. The common polysaccharides found in red seaweeds are agar, carrageenan, xylan, floridean starch, wate-soluble sulphated galactan and porphyrin. Green seaweeds contain sulfuric acid polysaccharide, sulfatedgalactan, and xylan and brown seaweeds contain alginic acid, fucoidan, laminarin and sargassum[8]. Some seaweeds such as galactan, fucoidan, laminarin, and alginate are present only in seaweeds[9]. So they are of great economic importance in industries such as stabiliser, emulsifier, food and beverages[10] .

Fatty acids: Fatty acids such as 20 carbon atoms polyunsaturated fatty acids present in seaweeds (especially in red seaweeds) are rich in 20 carbon atoms of polyunsaturated fatty acids named eicosapentaenoic and docosahexanoic[11, 12]. They are capable of oxidising PUFA (C20) by oxidative pathway and their two products are Gracilariales and prostaglandin. eicosanoid and its derivatives are received much more attention in research because of its anti-inflammatorydrugs[13].

Alginate or alginic acid and carrageenan are polysaccharide extracted from different red and brown seaweeds. Alginic acid contain 1,4-linked β-D-mannuronic acid and α-L-guluronic acid residues. Carrageenans are linear polysaccharides with half esters attached to sugar unit which are produced from red seaweeds (*Kappaphycus alvarezii* and *Eucheuma denticulatum*)[14]. Carageenans also have antitumor, antiviral, anticoagulant and immunomodulation properties besides being used as stabilizers in food industry[15, 16, 17]. Fucoidan is a polysaccharide found in brown seaweeds consisting of 10-20 % of dry weight of seaweeds. It contains L-fucose and sulfate ester groups[18]. High activity of anti coagulantion was exhibited by fucoidan extracted from *Ecklonia kurome*[19]. While *Laminaria angustata* exhibited high antithrombin activity[20]. Antiviral activity against Herpes simplex virus was observed by fucoidan[21, 22]. Brown seaweeds also possess another type of polysaccharide known as laminarins which are extracted from *Laminaria* species. It comprises of 10-30 % dry weight of seaweeds[4]. These laminarians are known to have probiotic, anticoagulant, and antioxidant properties[23, 4].

Phenolics and Phlorotannins: Brown seaweeds have high concentration of seaweeds as compared to green and red seaweeds. The content of phenol in seaweeds ranges from 1 % to 4% dry weight[4]. Phenolic compounds are bioactive such as phenylethanol and phenylethanol sulfate bromophenols isolated from red seaweed *Rhodomela confervoides* show moderate cytotoxicity against several cell lines, namely human colon cancer (HCT-8), hepatoma (Bel7402), stomach cancer (BGC -823), lung adenocarcinoma (A549) and human ovarian cancer (A2780)[24]. Phlorotannins are polymers of phloroglucinol having eight

phenol rings. They are produced by secondary metabolism in brown seaweeds having molecular size ranging from 400 to 400,000 Da exhibiting bioactivity. Phloroglucinol, eckol, and dieckol are three phlorotannins purified from brown seaweeds showed radical scavenging activity on H_2O_2 mediated DNA damage.

Proteins and Amino acids: Amino acids such as aspartic acid, glutamic acid and leucine are found in large amount in seaweeds while amino acids such as threonine, lysine, tryptophan, sulphur amino acids and histidine are found in lower amount in seaweeds[25]. Domoic acid isolated from *Chondria armata* (red seaweed) is a potent excitatory neurotransmitter and also a nitrogen atom containing heterocyclic compound. α-Kainic acid is an amino acid isolated from red seaweed *Digenea simplex* have a potent neurophysiology activity in mammals[26]. Kahalalides are sequences of amino and hydroxy carboxylic acid residues. Kahalalides A and F are polypeptides isolated from sacoglossan mollusk (*Elysia rufescens*), Elysiarufescens and green seaweed *Bryopsis* species[27]. These kahalalides are known to have antituberculosis activity which inhibits the growth of *Mycobacterium tuberculosis*[28].

Terpenes are secondary metabolites made up of isoprene units. Monoterpenes (two isoprene units) and sesquiterpenes (three isoprene units) are known to have bioactivity. Laurepinnacin and Isolaurepinnacin are acetylinic sesquiterpene ethers isolated from red seaweed *Laurencia pinnata*. They are potent toward Azuki bean beetle *Callosobruchus chinensis*[29]. Elatol is a halogenated sesquiterpene isolated from red seaweed *Laurencia dendroidea* which exhibits potent larvicidal effects against mosquito *Aedes aegypti*[30]. This compound also has antileishmanial, antitumor, acaricidal, and repellent activities[31, 32, 33]. Seaweeds are also rich source of diterpenes (four isoprene units). Antitumor activities, cytotoxicity activities, and antihelmintic effects were observed against earthworm *Allolobophora caliginosa* by diterpenes of the parguerene and isoparguerene series derived from red seaweed *Jania rubens*[34]. A meroterpenoid known as Sargaquinoic acid isolated from brown seaweed *Sargassum* are known to have antimalarial activity against chloroquine-sensitive strain (D10) of *Plasmodium falciparum*[35].

Seaweeds extracts and powder have shown bioactive effects such as antioxidant, peroxidation of fatty acids, antibacterial, antifungal and anti-inflammatory. It summarises that potential of biomolecules in seaweeds species can be utilized for health and food applications.

References:

1. Coppejans, E., Leliaert, F., Dargent, O., Gunasekara, R. and De Clerck, O. (2009) Sri Lankan seaweeds—methodologies and field guide to the dominant species. Abc Taxa 6(i-viii): 265.
2. Anantharaman, P. (2002) Manual on Identification of Seaweed.All India Coordinate Project on Survey and Inventorization of Coastal and Marine Biodiversity.J Mar Boil Assn Ind, 29: 1-9.
3. Sharma, O.P. (2011) Series on diversity ofmicrobes and cryptogams Algae. McGraw Hill, New Delhi.
4. Holdt, S.L. and Kraan, S. (2011) Bioactive compounds in seaweeds: functional food applications and legislation. J Appl Phycol, 23: 543–597.

5. Kumar, C.S., Ganesan, P. and Bhaskar, N. (2008) In vitro antioxidantactivities of three selected brown seaweeds of India. Food Chem, 107: 707–713.

6 Tseng, C.K. (2001) Algal biotechnology industries and research activities in China. J Appl Phycol, 13: 375–380.

7 Kumar, C.S., Ganesan, P., Suresh, P.V. and Bhaskar, N. (2008) Seaweeds as a Source of Nutritionally Beneficial Compounds—A Review. J of Food Sci and Tech, 45: 1-13.

8 Chandini, S., Kumar, G.P., Suresh, P.V., and Bhaskar, N. (2008) Seaweeds as source of nutritionally beneficial compounds—a review. J Food Sci Technol, 45(1):1–13.

9. Ferriera, L.G., Noseda, M.N., Gonalves, A.G., Ducatti, D.R.B., Fujii, M.T. and Duarte, M.E.R. (2012) Chemical strucute of the complex pyruvylated and sulfate-dagaran from the red seaweed *Palisada flagellifera* (Cermiales, Rhodophyta). Carbohydr Res, 347: 83–94.

10. Cardozo, K.H., Guaratini, T., Barros, M.P., Falcão, V.R., Tonon, A.P., Lopes, N.P., Campos, S., Torres, M.A., Souza, A.O., Colepicolo, P. and Pinto, E. (2007) Metabolites from algae with economical impact. Comp Biochem Physiol C Toxicol Pharmacol 146(1–2):60–78.

11. Stefanov, K., Konaklieva, M., Brechany, E.Y. and Christie, W.W. (1988) Fatty Acid Composition of Some Algae fromthe Black Sea. Phytochem27: 3495-3497.

12. Gerwick, W.H. and Bernart, M.W. (1993) Eicosanoids and Related Compounds from Marine Algae. In: Attaway, D.H. and Zaborsky, O.R., Eds., Mar Biotechnol1, Pharmaceutical and Bioactive Natural Products, Plenum Press, New York, 101-152.

13. Jacobs, R.S., Bober, M.A., Pinto, I., Williams, A.B., Jacobson, P.B. and de Carvalho, M.S. (1993) Pharmacological Studies of Novel Marine Metabolites. In Attaway, D.H. and Zaborsky, O.R., Eds., Advances in Marin Biotechnology: Pharmaceutical and Bioactive Natural Products, 1, Plenum Press, New York, 77-99.

14. Rasmussen, R.S. and Morrissey, M.T. (2007) Marine biotechnology for production of food ingredients. Adv Food Nutr Res, 52: 237–292.

15. Sen, A.K., Das, A.K., Banerji, N., Siddhanta, A.K., Mody, K.H., Ramavat, B.K., Chauhan, V.D., Vedasiromoni, J.R. and Ganguly, D.K. (1994) A new sulphated polysaccharides with potent blood anti-coagulant activity from the new seaweed *Grateloupia indica*. Int J Biol Macromol, 16: 279– 280.

16. Schaeffer, D.J. and Krylov, V.S. (2000) Anti -HIV activity of extracts and compounds from algae and cyano bacteria. Ecotoxicol Environ Saf, 45: 208–227.

17. Zhou, G.F., Sun, Y., Xin, H., Zhang, Y., Li, Z. and Xu, Z. (2005) In vivo antitumor and immunomodulation activities of different molecular weight lambda-carrageenans from *Chondrus ocellatus*. Pharmacol Res, 50: 47–53.

18. Li, B.., Lu, F., Wei, X. and Zhao, Z. (2008) Fucoidan: structure and bioactivity. Molecules, 13: 1671–1695.

19. Nishino, T. and Nagumo, T. (1987) Sugar constituents and blood-anticoagulant activities of fucose-containing sulfated

polysaccharides in nine brown seaweed species. Nippon Nogeikagaku Kaishi 61:361–363.

20. Kitamura, K., Matsuo, M. and Yasui, T. (1991) Fucoidan from brown seaweed *Laminaria angustata* var. *longissima*. Agric Biol Chem, 55(2): 615–616.

21. Hayashi, K., Nakano, T., Hashimoto, M., Kanekiyo, K. and Hayashi, T. (2008) Defensive effects of a fucoidan from brown alga *Undaria pinnatifida* against Herpes simplex virus infection. Int Immuno Pharmacol. 8: 109–116.

22. Hemmingson, J.A., Falshaw, R., Furneaux, R.H. and Thompson, K. (2006) Structure and antiviral activity of the galactofucan-sulfates extracted from *Undaria pinnatifida* (Phaeophyta). J Appl Phycol, 18: 185–193.

23. Chattopadhyay, N., Ghosh, T., Sinha, S., Chattopadhyay, K., Karmakar, P. and Ray, B. (2010) Polysaccharides from *Turbinaria conoides*: structural features and antioxidant capacity. Food Chem, 118: 823–829.

24. Ma, M., Zhao, J., Wang, S., Li, S., Yang, Y., Shi, J., Fan, X. and He, L. (2006) Bromophenols coupled with methyl gamma-ureidobutyrate, bromophenol sulfates from the red alga *Rhodomela confervoides*. J Nat Prod 69:206–210.

25. Dawczynski, C,, Schubert, R. and Jahreis, G. (2007) Amino acids, fatty acids, and dietary fibre in edible seaweed products. Food Chem, 103: 891– 899.

26. Rerkany, J.W. and Coyle, J.T. (1983) Kainic acid selectively stimulates the release of endogenous excitatory acidic amino acids. J Pharmacol Exp, 225: 399–406.

27. Bourel-Bonnet, L., Rao, K.V., Hamann, M.T. and Ganesan, A. (2005) Solid-phase total synthesis of Kahalalide A and related analogues. J Med Chem 48(5):1330–1335.

28. Hamann, M.T., Otto, C.S., Scheuer, P.J. and Dunbar, D.C. (1996) Kahalides: bioactive peptides from a marine mollusk, Elysia-rufescens and its algal diet Bryopsis sp. J Org Chem, 61: 6594–6600.

29. Fukuzawa, A. and Masamune, T. (1981) Laurepinnacin and isolaurepinnacin, new acetylenic cyclic ethers from the marine red alga *Laurencia pinnata* Yamada. Tetrahedron Lett, 22(41): 4081–4084.

30. Bianco, E.M., Pires, L., Santos, G.K.N., Dutra, K.A., Reis, T.N.V., Vasconcelos, E.R.T.P.P., Cocentino, A.L.M. and Navarro, D.M.A.F. (2013) Larvicidal activity of seaweeds from northeastern Brazil and of a halogenated sesquiterpene against the dengue mosquito (*Aedes aegypti*). Ind Crop Prod 43:270–275.

31. Dos Santos, A.O., Veiga-Santos, P., Ueda-Nakamura, T., Dias-Filho, B.P., Sudatti, D.B., Bianco, E.M., Pereira, R.C. and Nakamura, C.V. (2010) Effect of elatol, isolated from red seaweed *Laurencia dendroidea*, on *Leishmania amazonensis*. Mar Drugs, 8: 2733–2743.

32. Born, F.S., Bianco, É.M. and Da Camara, C.A.G. (2012) Acaricidal and repellent activity of terpenoids from seaweeds collected in Pernambuco, Brazil. Nat Prod Commun 7:463–466.

33. Campos, A., Souza, C.B., Lhullier, C., Falkenberg, M., Schenkel, E.P., Ribeirodo-Valle, R.M. and Siqueira, J.M. (2012) Anti-tumour effects of elatol, a marine

derivative compound obtained from red algae *Laurencia microcladia*. J Pharm Pharmacol 64(8):1146–1154.

34. Awad, N.E. (2004) Bioactive brominated diterpenes from the marine red alga *Jania rubens (L.) Lamx*. Phytother Res 18:275–279.

35. Afolayan, A.F., Bolton, J.J., Lategan, C.A., Smith, P.J. and Beukes, D.R. (2008) Fucoxanthin, tetraprenylated toluquinone and toluhydroquinone metabolites from *Sargassum heterophyllum* inhibit the in vitro growth of the malaria parasite *Plasmodium falciparum*. Z Naturforsch C 63:848–852.

Former insights into pathophysiology and treatment of Nephrotic syndrome: A short review

Bhoomi B. Joshi and Kinnari N. Mistry*

Ashok & Rita Patel Institute of Integrated Studies in Biotechnology & Allied Sciences (ARIBAS), New Vallabh Vidhya Nagar-388121 (Gujarat) India

Abstract: Nephrotic syndrome (NS) is a chronic kidney disorder, distinguished by modifications of glomerular filtration barrier, resulting in its incapability to control the urinary protein loss. NS is a pathological entity identified by massive proteinuria which can lead into mortal infections, thrombosis, and edema due to significant protein loss. Information about principal cause of a syndrome is necessary for accepting its mechanism and for its sufficient classification, prediction, and management. Currently, the etiologies of NS have been revealed due to various acquired as well as genetic defects and its progressive forms can lead to chronic and end-stage renal disease. Foremost breadth of view about pathophysiology and treatment of Nephrotic syndrome are reviewed.

Introduction

During of the 20th century attempts were made in the medical literature to distinguish nephrosis (i.e. kidney disease distinguished by exudation and proliferation) from nephritis (i.e. nephritis). But, when it was noticed that nephrosis is neither a single disease, nor a group of related diseases, the word "nephrosis" was replaced by "nephrotic syndrome"[1]. Clinically nephrotic syndrome (NS) features develops into rigorous proteinuria, hypoalbominemia, edema and hypercholesterol conditions. These circumstances are closely related to foremost structural and morphological changes in glomerular epithelial cells, also named as "podocytes". Podocytes are extremely specific cells with abundant foot processes that cover up the external aspect of the glomerular basement membrane (GBM). One of the vital purposes of kidney for the period of prime urine formation is ultrafilteration of plasma protein. Ordinary filtration task of the glomerulus relay on the structural and functional reliability of the filtration barricade, that is the chief target of numerous innate and acquired glomerular dysfunctions, distinguished by nephrotic syndrome (greater than 3.5 g protein per day) and swift development to end stage renal disease (ESRD)[2]. In the primary NS of size around 60-280 KDa plasma proteins are lost that makes remarkable changes in plasma protein level. Etiology says, NS is caused due to two main reasons (1) acquired (due to toxins or infection), and (2) genetics[3]. The total ontonic pressure and plasma protein level decides the secondary effects of NS, where plasma protein level goes up to 750g/l causing extension in plasma volume. In NS, there is thickening of the foot process, but the remaining of the cell generally is conserved[4]. Endothelial cells possess many outlets that are 65 to 95 nm in diameter, called fenestrae, which form a substantial barrier for passageway of

*Corresponding Author: sunilkhristi@aribas.edu.in

macromolecules from plasma into the renal tubule. Electron microscopy information leads to the recognition of negatively charged particles in the GMB, which prevent the passage of anionic macromolecules like albumin[5].

Epidemiology

NS can influence any age group, both children and adults as primary or secondary form of which 62% to 80% are glomerulonephritis cases, where as others are of secondary nephropathy. In US, occurrence of NS is 3-4 cases per 100,000 children per year[8]. Increasingly this has been gone up to 16 cases per 100,000 children. When compared it has been found more frequent among boys than girls of juvenile age groups, but once they reach at puberty there is no such noteworthy difference among genders. NS has been more frequently observed at the age of 2-14 among children. Research proved Enlarged prevalence and extreme disease condition in African American and Hispanic populations[6]. There are also differences in epidemiology between the colours, the disease is more general in black than in white by a ratio of 2 to 1.The incidence data also states knowledge related to the majority widespread way that symptom develops in patients with NS as unprompted remission happens in up to 25% to 35% of cases during the initial year of the illness[7]. On the other hand, this improvement is not classic as some 55% to 65% of patients dies and / or expand to unrelieved renal failure 7 to 14 years after this remission. The main causes of death are cardiovascular, as a result of the chronicity of the syndrome, and thromboembolic accidents[8].

Pathophysiology

In NS, the pathophysiology of normal glomerular filtration function is strongly interrupted, resulting in severe-range proteinuria and hypoalbumina conditions. Reports showed role of immune pathogenesis where defect in T-Cell occurs through various circulating factors such as cytokines and other molecules[9,10]. On the whole, the glomerular filtration barrier is made of three consecutive layers, scheduled from capillary side to bowman's space side: Fenestrated endothelium negatively charged basement membrane to prevent the passage of large anionic molecules, visceral epithelial called as podocytes, which contains small pores with a fixed size with radius of around 30 to 50 amperes connecting adjacent foot processes are bridge by slit diaphragms and further maintain structural and function integrity of GMB[11]. In NS, the glomeruli are unable to filter back. NS pathophysiology revel protenuria, here the glomeruli are affected by inflammation or hyalinization and are unable to filter back albumin or other immunoglobulins back into blood rather these molecules pass through the membrane and are found in urine. Albumin is the major blood protein that regulates plasma ontonic pressure which causes increase in hepatic lipoprotein and transcapillary water level which later on causes the hyperlipidemia and edima conditions linked with NS. The actual mechanism by which this glomerular membrane gets damaged in primary and secondary disease is unknown, but reports chains the role of T-cells in up regulating circulating factors or down regulating inhibitory factors in reaction to unrevealed immunogens and cytokines[12]. Other probable facts involved in pathophysiology of NS can be either hereditary defect in proteins that are essential to the slit diaphragms such as Nephrin and podocin or activation of cell complementary system causing damage and loss of the negatively charged groups attached to proteins of the GBM.

A diverse metabolic consequence of proteinuria includes, Infection, Hypocalcemia and bone abnormalities, Hypercoagulability and Hypovolemia. During infections patients are more susceptible to Varicella infection along with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*. The most common infectious complications are bacterial sepsis, cellulitis, pneumonia, and peritonitis[13]. NS patients are very frequently affected by hyopocalcemia conditions caused by low serum albumin level; on the other hand low bone density and abnormal bone histology are also reported. Urinary losses of vitamin D–binding proteins with subsequent hypovitaminosis D are one of the reason of such circumstances where reduced in intestinal calcium absorption occurs[14]. It is probable that long duration of either this syndrome or its treatments are the significant risk factors for bone disease in these patients. Venous thrombosis and pulmonary embolism are eminent complications of NS, in these patients urinary loss of anticoagulant proteins, like antithrombin III and plasminogen, beside synchronized raise in clotting factors, particularly factors I, VII, VIII, and X causes conditions such as Hypercoagulability[22]. A report by Mahmoodi et al confirmed the increase in venous thromboembolism (VTE) and arterial thrombotic events together with coronary and cerebrovascular ones with 10 to 15 times higher effect in NS patients compare to normal ones. Acute renal malfunction may point to a fundamental glomerulonephritis however it is more frequent causes of hypovolemia or sepsis. All these consequences finally results to Hypertension connected fluid retention and reduced kidney function which may develop in patients with chronic end stage renal disease[22,23].

Signs and Symptoms

The universal sign and manifestation of NS are swelling, weight gain, fatigue, blood clots, and infections where as some patients may develop kidney failure. Due to increase in protein excretion the urine in the toilet bowel may direct to frothy appearance[25]. This injure where protein usually leak in the urine in more quantity, reduces the total blood protein level. In view of the fact that the protein in the blood prompts the flow of liquid in the bloodstream, due to low protein level this fluid leak out of into tissues, causing swelling, and called edema[15]. The swelling is mainly visible in legs and around eyes when the patients first get up in the morning, in due course of time this swelling may be there all the time and arise in other body parts too along with rapid weight gain[16]. Very less number of patient's are found to have weight loss and this may be due to malnutrition or an principal circumstances, such as badly controlled diabetes mellitus, a chronic viral infection, or cancer. Gradually NS develops in kidney dysfunction, with no or less symptoms at early stage but conversely kidney function continues to worsen finally developing end stage renal disease symptoms, with shortness of breath, weakness and easy fatigability (from anemia) and loss of appetite[17].

The concentration of lipids especially cholesterol and/or triglycerides can become greatly elevated in patients causing increase in risk of coronary artery disease[18]. Patients with NS are at greater risk of blood clots in the veins or arteries which travel through lungs which leads to dangerous and fatal stage. Patients with severe NS are at increased danger for infections, even though the reasons for this are

not well understood. Simple test includes urine visualization where urine foams more than normal because of the quantity of protein in it. Diagnosis may also require a kidney biopsy[29].

Treatment and management

Patients who show positive with signs and symptoms of intense assault are supposed to be treated straight away in an intensive care setting. Current studies confirmed the effectiveness of intravenous theophylline in dropping the period and intense leaky phase of an acute NS. Different vasopressors drugs, for example, 260 mL of a 20% albumin-containing solution, given over 20-60 minutes at intervals determined by clinical status, which have been found to be more successful in maintaining hemodynamic stability among patients[30]. Corticosteroid therapy to counter the inflammatory triggers has now a day's occasionally stopped or minimized as it has been believed that steroids may be damaging to patients who face more frequent attacks and even the affect steroid course in subsequent episodes is uncertain. Many people who go through more severe attacks require mechanical ventilation because of flash pulmonary edema[19,20].

The main goals of cure are to reduce symptoms, avoid complications, and hinder end-stage renal damage. Here are few commonly used treatments enlisted below used to control NS by treating the disorder that is causing it.Use of ACE inhibitors i.e. Angiotensin converting enzyme, to diminish proteinuria, and decrease the threat of evolution to renal disease in persons with NS. In some patient's steroids are given along with ACE inhibitors and maintaining blood pressure at or below 120/80 mmHg to improve response. The suggested dose is unclear; the actual dosage varies from patient to patient. Keep blood pressure at or below 130/80 mmHg to delay kidney damage[21].

Treatment with corticosteroids remains different among adults and children and is more clearly proved that children respond well compare to grownups, in some patient's it is beneficial while others do not respond at all. Previous studies prove that patients with minor rigorous glomerular changes responded well to steroids treatment. It is recommended that family physicians must consult with nephrologists whether treatment with corticosteroids is sensible, on the contrary the indecisive benefits and chance of adverse effects. Use of alkylating agents has few less proof for improving disease condition, but may be considered for patients who do not respond to corticosteroids[22].

Studies are going on to inspect the benefits and problems of lipid-lowering treatments in NS. A number of confirmations suggested an enlarged hazard of atherogenesis or myocardial infarction in patients with NS, perhaps connected to increased lipid levels. Lipid lowering treatment is used to treat high cholesterol to decrease the risk of heart and blood vessel problems and for that medication to decrease cholesterol and triglycerides are usually needed[23].

Along with all these therapies doctors recommended few antibiotic and anticoagulating treatments deepening upon patients response to NS. A low-salt and low-protein diet may help with swelling in the hands and legs and control adverse effects of protenuria[24,25].

References

1. Arneil, G.C., Clin North Am **18**, 547-59 (1971).
2. Arneil, G.C., Lam, C.N., Lancet **2**, 819-21 (1966).
3. ISKDC, J Pediatr **98**, 561-64 (1981).
4. Smoyer, W.E., Mundel P., J Mol Med (Berl) **76**, 172-83 (1998).
5. Dantal, J. *et al*., N. Engl. J. Med **330**, 7-14 (1994).
6. Srivastava, T., Simon, S.D., Alon, U.S., Pediatr Nephrol **13**, 13-18 (1999).
7. Hogg, R.J. *et al*., Pediatrics **105**, 1242-49 (2000).
8. McEnery, P.T., Strife, C.F., Pediatr Clin North Am **29**, 875-94 (1982).
9. Bonilla-Felix M. *et al*., Kidney Int **55**, 1885-90 (1999).
10. Kari J.A., Saudi Med J **23**, 317-21 (2002).
11. Appel, G.B., *Engl J Med* **312**, 1544-8 (1985).
12. Curry, R.C. *et al*., *Am J Med* **63**, 183-92 (1977).
13. Mittal, S.K. *et al*., *Kidney Int* **55**, 1912-9 (1999).
14. Tessitore N.*et al., Nephron* **37**, 153-9 (1984).
15. Gulati S, *et al., Am J Kidney Dis* **41**, 1163-9 (2003).
16. Leonard M.B., *et al*., *N Engl J Med* **351**, 868-75 (2004).
17. Ichikawa, I. et al., J Clin Invest **71**, 91-103 (1983).
18. Vande Walle J.G. *et al*., Pediatr Nephrol **16**, 283-93 (2001).
19. Garin, E.H., Pediatr Nephrol **14**, 872- 78 (2000).
20. Van den Berg, J.G., Weening, J.J., Clin Sci (Lond) **107**, 125-36 (2004).
21. ISKDC, Kidney Int **13**, 159-65 (1978).
22. Sorof, J.M. *et al*, Pediatr Nephrol **12**,764-68 (1998).
23. Brater, D.C., N Engl J Med 339, 387-95


"We
are committed to nation
through our quality teaching
and research keeping students in
focus along with involvement of
our employees and continual
improvement in all areas."
ज्ञानेन शीलम्
ARIBAS
A CVM Institute

ज्ञानेन शीलम्

Do send us your comments and suggestion at e-mail:

quest@aribas.edu.in

ASHOK & RITA PATEL INSTITUTE OF INTEGRATED STUDY & RESEARCH IN BIOTECHNOLOGY AND ALLIED SCIENCES

P.O. Box No. 61, New Vallabh Vidyanagar, Vitthal Udyognagar - 388121, Dist- Anand, Gujarat, India.

Phone: +91-2692-229189, 231894 Fax: +912692-229189