



## APPENDIX B

# RESEARCH ARTICLES IN SUPPORT OF RESPIGARD™ EFFICACY: RESPIRATORY & IMMUNE SYSTEM SUPPORT

(Respigard™ Active Ingredient: Rhizophora mangle L.  
in a base of vegetable glycerin)

**THE GLOBAL RESEARCH ON THE EFFECTS OF** red mangrove extracts and some of its primary active phytochemical compounds is extensive. A synthesis of a subset of the research can be summarized as follows:

“The phytochemical constituents and whole component parts of red mangrove (Rhizophora mangle, L.) are known to provide anti-microbial, anti-inflammatory, immune-modulating, anti-pyretic, and anti-oxidant functions. Some of the primary constituents are Complex Polysaccharide Compounds, Salicylates, and Polyphenols & Phytos-

terols including specified tannic acids and members of the sub-class of polyphenols known as Flavonoids: Quercitin, Umbelliferone (7-hydroxycoumarin), Luteolin, Kaempferol, and Isorhamnetin.”

**Ted D. Anders, Ph.D.**

**The FDA-compliant botanical structure/function statement for Respigar<sup>TM</sup>:**

**“Supports Respiratory and Immune Systems Function...  
...during Seasonal and Ongoing Challenges”**

**Research Bibliography  
(presented by general metabolic activity)  
Upper Respiratory Infection References**

1. Carroll, Scott , “The effect of Fijian Red Mangrove (*Rhizophora mangle*) on the common cold,” Atlanta Allergy & Asthma Institute and Nature’s Nurse, Inc., published online January 5, 2006, [www.naturesnurse.com/research](http://www.naturesnurse.com/research), 1-4.
2. Doseff, A. I., Arango, D., Cardenas, H. Nicholas, C., Nuova, G., Grotewold, E., “Thematic Poster Session—Novel Therapeutic Options in Airways Disease,” *American Journal of Respiratory and Critical Care Medicine* (2011).
3. Heinz, S.A., Henson, D.A., Austin, M.D., Jin, F., Nieman, D.C., “Quercitin supplementation and upper respiratory tract infection: A randomized clinical trial,” *Pharmacological Research* 62(3): 237-242.

4. Trivedi, R., Anders, T.D., et. al., “The effect of red mangrove aqueous extract (*Rhizophthora mangle*, L.) on Upper Respiratory Tract Infections (URTI),” published online April, 2012, by Nature’s Nurse International, Inc., [www.naturesnurse.com/research](http://www.naturesnurse.com/research).
5. Yi, L., Li, Z., et al, “Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells,” *Journal of Virology* (2004): 11334-11339.

## Immune System Modulation References

6. Chunchao, H., Guo, J., “A hypothesis: supplementation with mushroom-derived active hexose correlated compound modulates immunity and increases survival in response to influenza virus (H1N1) infection,” *Evidence-Based Complementary and Alternative Medicine* (2011): 1-3.
7. Reynolds, J.A., Kastello, M.D., Harrington, D. G., Crabbs, C.L., Peters, C. J., Jemenksi, J.V., Scott, G.H., Di Luzio, N.R., “Glucan-induced enhancement of host resistance to selected infectious diseases,” *Infection and Immunity* (1980): 51-57.
8. Ritz, B.W., Nogusa, S., Ackerman, E. A., Gardner, E., “Supplementation with active hexose correlated compound increases the innate immune response of young mice to primary influenza infection,” *American Society for Nutrition* (2006): 2868-2873.
9. Ritz, B. W., 2011, “Fermented mushroom extract affects immune outcomes and immune cell populations,” *Enzyme Science*, published online Jan 1, 2011, 1-7.
10. Spierlings, L.H. E., Fujii, H., Buxiang, S., Walshe, T., “A phase study of the safety of the nutritional supplement, active hexose

- correlated compound, AHCC, in healthy volunteers,” *Journal of Nutritional Science and Vitaminology*, 53 (2007): 536-539.
11. Tzianabos, A., O., “Polysaccharide immunomodulators as therapeutic agents: structural aspects and biologic function,” *Clinical Microbiology Reviews* (2000): 523-533.

## **Anti-Microbial Constituent References and Mangrove Component References**

12. Basile. A., Giordano, S., Lopez-Saez, J.A., Cobianchi, R. C., “Antibacterial activity of pure flavonoids isolated from mosses,” *Phytochemistry* 52 (1999):1479-1482.
13. Chandrasekaran, M., Kannathasan, K., Venkatesalu, V., Prabhakar, K., “Antibacterial activity of some salt marsh halophytes and mangrove plants against methicillin resistant Staphylococcus aureus,” published online October, 2008, Springer-Science + Business Media B.V.
14. de Armas, E., Sarracent, Y., Marrero, E., Fernandez, O., Branford-White, C., “Efficacy of Rhizophora mangle aqueous bark extract (RMABE) in the treatment of aphous ulcers: a pilot study,” *Current Medical Research and Opinion* 21(11) (2006): 1711-1715.
15. Hicks, M., Bailey, M.A., Thiagarajan, T.R., Troyer, T. L., Huggins, L.G., “Antibacterial and Cytotoxic Effects of Red Mangrove (Rhizophora Mangle L. Rhizophoraceae) Fruit Extract,” *European Journal of Scientific Research* 63(3) (2011): 439-446.
16. Lyu,S., Rhim, J., Park, W., “Antiherpetic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro,” *Archives of Pharmacology Research* 28/11 (2005): 1293-1301.

17. Melchor, G., Armenteros, M., Fernández, O., Linares, E., Fragas, I., "Antibacterial activity of Rhizophora mangle bark," *Fitoterapia* 72 (6) (2001): 689-691.
18. Ravikumar, S., Inbaneson, S. J., Suganthi, P., Venkatesan, M., and Ramu, A., "Mangrove plants as a source of lead compounds for the development of antiplasmodial drugs from South East coast of India", *Parasitol Research* 108 (2011): 1405-1410.
19. Sanchez Perera, M.L., Varcalcel, L., Escobar, A., Noa, M., "Polyphenol and Phytosterol Composition in an Antibacterial Extract from Rhizophora mangle," L. Bark, *Journal of Herbal Pharmacotherapy*, 7(3-4) (2007).
20. Tsai, F., Lin, C., Lai, C., Lan, L., Lai, C., Hung, C., Hsueh, K., Lin, T., Chang, H., Wan, L., Jinn-Chyuan Sheu, J., and Ying-Ju Lin. "Kaempferol inhibits enterovirus 71 replication and internal ribosome entry site (IRES) activity through FUBP and HNRN proteins," *Food Chemistry* 128(2) (2011): 312-322.

## Anti-Inflammatory Constituent References

21. Calderón-Montaño, J., Burgos-Morón, E., Pérez-Guerrero, C. and M. López-Lázaro, "A Review on the Dietary Flavonoid Kaempferol," *Mini-Reviews in Medicinal Chemistry* 11 (2011): 298-344.
22. Cho, S., Park, S., Kwon, M., Jeong, T., Bok, S., Choi, W., Jeong, W., Ryu, S., Do, S., Lee, C., Song, J., Jeong, K. "Quercetin suppresses proinflammatory cytokine production through MAP kinases and NF-κB pathway in lipopolysaccharide-stimulated macrophage," *Molecular and Cellular Biochemistry* 243 (2003): 153–160.

23. Courtney, N., 2012, "The anti-inflammatory mechanisms of the flavonoid apigenin in vitro and in vivo," OhioLINK ETD Center, July 2012, [http://rave.ohiolink.edu/etdc/view?acc\\_num=osu1259783472](http://rave.ohiolink.edu/etdc/view?acc_num=osu1259783472), 1-2.
24. García-Mediavilla, V., Crespo, I., Collado, P., Esteller, A., Sánchez-Campos, S., Tuñón, M., González-Gallego, J. "The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells," *European Journal of Pharmacology* 557(2-3) (2007):221-229.
25. Jang, S., Kelley, K., and R. W. Johnson. "Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1," *Proceedings of the National Academy of Sciences* 105(21) (2008): 7534-7539.
26. Karlsem, A., Rettersol, L., Laake, P., Paur, I., Kjolsrud-Bohn, S., Sandvik, L., Blomhoff, R, "Anthocyanins inhibit nuclear factor-kB activation in monocytes and reduce plasma concentrations of pro-inflammatory mediators in healthy adults," *Journal of Nutrition* 137 (2007): 1951-1954.
27. Kelly, G. S., Quercetin Monograph, *Alternative Medicine Review* 16(2) (2011): 172-194.
28. Lino, C. S., Taveira, M. L., Vianaw, G. S. B., and F. J. A. Matos. "Analgesic and Anti-inflammatory Activities of *Justicia pectoralis* Jacq and its Main Constituents: Coumarin and Umbelliferone," *Phytotherapy Research*, 11 (1997): 211–215.
29. López-Lázaro, M. "Distribution and Biological Activities of the Flavonoid Luteolin," *Mini-Reviews in Medicinal Chemistry* 9 (2009): 31-59.
30. Nicholas, C., Batra, S., Vargo, M. A., Voss, O. H., Gavrilin, M. A., Wewers, M.D., Guttridge, D.C., Grotewold, E., Doseff,

- A.I., "Apigenin blocks lipopolysaccharide-induced lethality in vivo and proinflammatory cytokines expression by inactivating NF- $\kappa$ B through suppression of p65 phosphorylation," *The Journal of Immunology* 179: 7121-7127.
31. Taís A. de Almeida Barrosa, Luis A.R. de Freitas, José M.B. Filhob, Xirley P. Nunesb, Ana M. Giuliettic, Glória E. de Souzad, Ricardo R. dos Santosa,e, Milena B.P. Soaresa,e and Cristiane F. Villarreal, "Antinociceptive and anti-inflammatory properties of 7-hydroxycoumarin in experimental animal models: potential therapeutic for the control of inflammatory chronic pain," *Journal of Pharmacy and Pharmacology* 62 (2010): 205–213.
32. Theoharides, T. "Luteolin as a therapeutic option for multiple sclerosis," *Journal of Neuroinflammation* 6 (2009): 29-31.
33. Yoon,J., Lee, H., Choi, S., Chang, E., Lee, S., Lee, E. "Quercetin Inhibits IL-1b-Induced Inflammation, Hyaluronan Production and Adipogenesis in Orbital Fibroblasts from Graves' Orbitopathy," *PLoS ONE* 6(10) (2011): 1-10.

## Anti-Oxidant Constituent References

34. Berenguer, B., Sanchez, L.M., Quilez, A., Lopez-Barreiro, M., de Haro, O., Galvez, J., and Martin, M. J., "Protective and Antioxidant effects of Rhizophora mangle, L. against NSAID-induced gastric ulcers," *Journal of Ethno-Pharmacology* 103 (2006), 194-200.
35. Fabiani, R., Rosignoli, P., De Bartolomeo, A., Fuccelli, R., Servili, M., Montedoro, G. F., Morozzi, G., "Oxidative DNA damage is prevented by extracts of olive oil, hydroxytyrosol, and other olive phenolic compounds in human blood mono-

- nuclear cells and HL60 cells," *Journal of Nutrition* 138 (2008): 1411-1416.
36. Sánchez, J., Melchor, G., Martínez, G., Escobar, A., Faure, R., "Antioxidant activity of Rhizophora mangle bark," *Fitoterapia*, Vol. 77, Issue 2 (2006): 141-143.
37. Sanchez, M., Lodi, F., Vera, R., Villar, C., Cogolludo, A., Jimenez, R., Moreno, L., Romero, M., Tamargo, J., Perez-Vizcaino, F., and J. Duarte, "Quercetin and Isorhamnetin Prevent Endothelial Dysfunction, Superoxide Production, and Overexpression of p47phox Induced by Angiotensin II in Rat Aorta," *Journal of Nutrition* 137 (2007): 910-915.
38. Zielińska, M., Kostrzewska, A., Ignatowicz, E., and J. Budzianowski, "The flavonoids, quercetin and isorhamnetin 3-O-acylglucosides diminish neutrophil oxidative metabolism and lipid peroxidation," *Acta Biochimica Polonica* 48(1) (2001): 183-189.



## APPENDIX C

# RESEARCH ARTICLES IN SUPPORT OF SKINGARD™ EFFICACY

(SkinGard™ Active Ingredient: Rhizophora mangle L.  
in a base of vegetable glycerin)

**THE GLOBAL RESEARCH ON THE EFFECTS OF** red mangrove extracts and some of its primary active phytochemical compounds on skin health is extensive. A synthesis of the research can be summarized in the following FDA-compliant statement:

**“Botanical Structure/Function Statement:  
SkinGard™ Supports Healthy Skin Tissue ...”**

The product is used during a variety of minor accidental, post-surgical, environmental, and natural challenges to skin health ... while also providing anti-oxidants which are known to provide anti-aging support.

**Dr. Ted Anders**

## Research Bibliography

1. Berenguer, B., Sanchez, L.M., Quilez, A., Lopez-Barreiro, M., de Haro, O., Galvez, J., and Martin, M. J., "Protective and Antioxidant effects of Rhizophora mangle, L. against NSAID-induced gastric ulcers," *Journal of Ethno-Pharmacology* 103 (2006): 194-200.
2. Chandrasekaran, M., Kannathasan, K., Venkatesalu, V., Prabhakar, K. "Antibacterial activity of some salt marsh halophytes and mangrove plants against methicillin resistant Staphylococcus aureus," Springer-Science + Business Media B.V., published online October 19, 2008.
3. Cho, S., Park, S., Kwon, M., Jeong, T., Bok, S., Choi, W., Jeong, W., Ryu, S., Do, S., Lee, C., Song, J., Jeong, K., "Quercetin suppresses proinflammatory cytokine production through MAP kinases and NF-κB pathway in lipopolysaccharide-stimulated macrophage," *Molecular and Cellular Biochemistry* 243:(2003):153–160.
4. de Armas, E., Sarracent, Y., Marrero, E., Fernandez, O., Branford-White, C., "Efficacy of Rhizophora mangle aqueous bark extract (RMABE) in the treatment of aphous ulcers: a pilot study," *Current Medical Research and Opinion* 21(11) (2006): 1711-1715.
5. Fernandez, O., Capdevila, J. Z., Dalla, G., Melchor, G., "Efficacy of Rhizophora mangle aqueous bark extract in the healing of open surgical wounds," *Fitoterapia* Vol. 73, Issues 7–8 (2002): 564-568.
6. Gleiby Melchor, Mabelin Armenteros, Octavio Fernández, Eliana Linares, Ivis Fragas, "Antibacterial activity of Rhizophora mangle bark," *Fitoterapia* Vol. 72, Issue 6 (2001): 689-691.

7. Hicks, M., Bailey, M.A., Thiagarajan, T.R., Troyer, T. L., Huggins, L.G., "Antibacterial and Cytotoxic Effects of Red Mangrove (*Rhizophora Mangle* L. *Rhizophoraceae*) Fruit Extract," *European Journal of Scientific Research* 63(3) (2011): 439-446.
8. Kelly, G. S., Quercetin Monograph, *Alternative Medicine Review* 16(2) (2011):172-194.
9. List, R., Patent Application Document, Application Number: EP2010/053096. An adhesive patch according to any one of claims 2 and 4, wherein said at least one therapeutic agent comprises red mangrove. (Herpes treatment), 2011.
10. Lyu, S., Rhim, J., Park, W., "Antiherpetic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro, *Archives of Pharmacology Research* 28/11 (2005): 1293-1301.
11. Marrero, E., Sánchez, J., de Armas, E., Escobar, A., Melchor, G., Abad, M.J., Bermejo, P., Villar, A.M., Megías, J., Alcaraz, M.J., "COX-2 and sPLA<sub>2</sub> inhibitory activity of aqueous extract and polyphenols of *Rhizophora mangle* (red mangrove)," *Fitoterapia* Vol. 77, Issue 4, (2006): 313-315.
12. Meira de-Faria, F., Alves Almeida, A.C., Luiz-Ferreira, A., Dunder, R.J., Takayama,C., Silene da Silva, M., Aparecido da Silva, M., Vilegas, W., Rozza, A. L., Pellizzon, C. H., Toma, W., Monteiro Souza-Brito, A.G., "Mechanisms of action underlying the gastric antiulcer activity of the *Rhizophora mangle* L.," *Journal of Ethnopharmacology* Vol. 139, Issue 1 (2012): 234-243.
13. Sánchez, J., Melchor, G., Martínez, G., Escobar, A., Faure, R., Antioxidant activity of *Rhizophora mangle* bark," *Fitoterapia* Vol. 77, Issue 2 (2006) : 141-143.
14. Sanchez Perera, M.L., Varcalcel, L., Escobar, A., Noa, M., "Polyphenol and Phytosterol Composition in an Antibacterial

- Extract from Rhizophora mangle, L. Bark," *Journal of Herbal Pharmacotherapy*, Vol. 7 (2007): 3-4.
15. Vu Huong Giang, Le Quynh Lien, Ninh Khac Ban, Chau Van Minh, "Evaluation of Bacteria Inhibitory Activity of Mangrove Flora in Xuan Thuy National Park," *Bio Magazine* 35-3 (2013): 342-347

## Research Relevant to Wounds & Lesions

1. Berenguer, B., Sanchez, L.M., Quilez, A., Lopez-Barreiro, M., de Haro, O., Galvez, J., and Martin, M. J., "Protective and Antioxidant effects of Rhizophora mangle, L. against NSAID-induced gastric ulcers," *Journal of Ethno-Pharmacology* 103 (2006): 194-200.
2. Chandrasekaran, M., Kannathasan, K., Venkatesalu, V., Prabhakar, K., published online October 19, 2008, "Antibacterial activity of some salt marsh halophytes and mangrove plants against methicillin resistant *Staphylococcus aureus*," Springer-Science + Business Media B.V.
3. Cho, S., Park, S., Kwon, M., Jeong, T., Bok, S., Choi, W., Jeong, W., Ryu, S., Do, S., Lee, C., Song, J., Jeong, K., "Quercetin suppresses proinflammatory cytokine production through MAP kinases and NF-κBpathway in lipopolysaccharide-stimulated macrophage." *Molecular and Cellular Biochemistry* 243 (2003): 153–160.
4. de Armas, E., Sarracent, Y., Marrero, E., Fernandez, O., Bradford-White, C, "Efficacy of Rhizophora mangle aqueous bark extract (RMABE) in the treatment of aphous ulcers: a pilot study," *Current Medical Research and Opinion* 21(11) (2006): 1711-1715.

5. Fernandez, O., J.Z Capdevila, G Dalla, G Melchor, "Efficacy of Rhizophora mangle aqueous bark extract in the healing of open surgical wounds," *Fitoterapia* Vol. 73, Issues 7–8 (2002): 564-568.
6. Gleiby Melchor, Mabelin Armenteros, Octavio Fernández, Eliana Linares, Ivis Fragas, "Antibacterial activity of Rhizophora mangle bark," *Fitoterapia* Vol. 72, Issue 6 (2001): 689-691.
7. Hicks, M., Bailey, M.A., Thiagarajan, T.R., Troyer, T. L., Huggins, L.G "Antibacterial and Cytotoxic Effects of Red Mangrove (Rhizophora Mangle L. Rhizophoraceae) Fruit Extract," *European Journal of Scientific Research*, 63(3) (2011): 439-446.
8. Kelly, G. S., Quercetin Monograph, *Alternative Medicine Review* 16(2) (2011):172-194.
9. List, R., Patent Application Document, Application Number: EP2010/053096. An adhesive patch according to any one of claims 2 and 4, wherein said at least one therapeutic agent comprises red mangrove (Herpes treatment), 2011.
10. Lyu,S., Rhim, J., Park, W., "Antiherpetic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro," *Archives of Pharmacology Research*, 28/11 (2005): 1293-1301.
11. Marrero, Evangelina, Janet Sánchez, Elizabeth de Armas, Arturo Escobar, Gleiby Melchor, M.J. Abad, Paulina Bermejo, Angel M. Villar, J. Megías, María J. Alcaraz, "COX-2 and sPLA<sub>2</sub> inhibitory activity of aqueous extract and polyphenols of Rhizophora mangle (red mangrove)," *Fitoterapia* Vol. 77, Issue 4 (2006): 313-315.
12. Meira de-Faria, Felipe, Ana Cristina Alves Almeida, Anderson Luiz-Ferreira, Ricardo José Dunder, Christiane Takayama, Maria Silene da Silva, Marcelo Aparecido da Silva, Wagner Vilegas, Ariane Leite Rozza, Cláudia Helena Pellizzon, Walber

- Toma, Alba Regina Monteiro Souza-Brito, "Mechanisms of action underlying the gastric antiulcer activity of the Rhizophora mangle L.," *Journal of Ethnopharmacology* Vol. 139, Issue 1 (2012): 234-243.
13. Odio, A. D., Gonzalez, J. E., Sanchez, M. L., Delgado, N. G., "Genotoxic assessment of aqueous extract of Rhizophora mangle L. (mangle rojo) by spermatozoa head assay," published online: [http://bvs.sld.cu/revistas/pla/vol\\_15\\_1\\_10/pla03110.htm](http://bvs.sld.cu/revistas/pla/vol_15_1_10/pla03110.htm).
14. Sánchez, Janet, Gleiby Melchor, Gregorio Martínez, Arturo Escobar, Roberto Faure. "Antioxidant activity of Rhizophora mangle bark," *Fitoterapia* Vol. 77, Issue 2 (2006): 141-143.
15. Sanchez Perera, M.L., Varcalcel, L., Escobar, A., Noa, M., "Polyphenol and Phytosterol Composition in an Antibacterial Extract from Rhizophora mangle, L. Bark," *Journal of Herbal Pharmacotherapy*, Vol. 7 (3-4) (2007).