Prolific Drug Discovery – Anti Viral And Immunomodulatory- Focusedon Sars-Cov 2 And Therapeutic Significance

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***Abstract*—The corona Virus, though not "Pandemic" but has opened its deadly wings in series of Countries, which alarming.**

During infection with corona viruses, as with all other RNA viruses, replication of genome and transcription of mRNAs must occur. Replication of the genome involves the synthesis of a full-length negative-strand RNA that is present at a low concentration and serves as template for full-length genomic RNA.

The current model is that discontinuous transcription occurs during the synthesis of subgenomic negative-strand RNAs, with the antileader sequences being added onto the 3′ ends of negative-strand RNAs which then serve as templates for synthesis of mRNAs Corona viruses attach to specific cellular receptors via the spike protein

Keywords—SARS, Cov 2, Plants and composition, Pandemic, DNA, RNA, coat of protein, Pathogenesis

PREFACE:

Man's existence on this earth has been made possible only because of the vital role played by the plant kingdom in sustaining his life. Without the variety of living organisms that makes up the World of plants, animal life would not survive and our planet would have been a barren and lifeless World of deserts. The nature has showered a complete store-house of remedies to cure all ailments of mankind. Since the dawn of civilization, in addition to food crops, man cultivated herbs for his medicinal needs. The knowledge of drugs has accumulated over thousands of years as a result of man's inquisitive nature. The human beings appear to be afflicted with more diseases than any other animal species.

Tropical forest plants have served as a source of medicines for people of the tropics for millennia. We are well aware of the number of modern therapeutic agents that have been derived from tropical forest species. It is a fact of history that around 120 pharmaceutical products have been derived from plants and some 75% of these were discovered by examining the use of these plants in traditional medicine.

DEFINITION OF VIRUS:

Viruses are very small infectious agents. They're made up of a piece of genetic material, such as DNA or RNA, that's enclosed in a coat of protein. Viruses invade cells in your body and use components of those cells to help them multiply. This process often damages or destroys infected cells. A viral disease is any illness or health condition caused by a virus.

INTRODUCTION – c o v i d 19

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The heptad repeat domains and the putative fusion peptide are believed to play important roles in the fusion process

SARS infection exhibits a wide clinical course, characterized mainly by fever, dyspnoea, lymphopenia, and lower respiratory tract infection like other RNA viruses; all corona viruses encode, in addition to structural proteins and replicase proteins, small nonessential proteins of unknown function.

In addition to its role as structural protein, N protein plays a role in transcription and also in pathogenesis. Expression of N protein is necessary for efficient recovery of virus from infectious cDNA clones and recently has been shown to enhance the replication of HCoV-229E genome RNA.

The M protein (Membrane Protein) is the most abundant virion membrane protein. Aside from its role in viral assembly, the coronavirus M protein is believed to have functions in host interactions. It may be O glycosylated (groups I and III) or N glycosylated (group II). While glycosylation is not essential for viral

assembly or infectivity, the glycosylation state of M protein is likely to play a role in virus-host interaction.

PATHOGENESIS:

The family *Coronaviridae* contains two separate genera: corona viruses and toroviruses. Corona viruses are found in a wide range of animal species. In humans, corona viruses are mainly respiratory pathogens, although they have been occasionally shown to be the cause of some cases of diarrhoea. Before the SARS epidemic, only two human corona viruses had been characterized (HuCoV-229E and HuCoV-OC43). Both of these usually cause a mild upper respiratory tract infection.

Corona viruses are large lipid-enveloped, positive-sense, single-stranded RNA viruses, approx. 30 kb in length and are the largest RNA viruses known. The virus codes for several proteins, including an RNA-dependent RNA polymerase (Pol), a surface spike glycoprotein (S protein), which attaches the virus to a host cell and is the target for neutralizing antibodies [8,9], a small envelope protein (E), a membrane glycoprotein (M) and a nucleocapsid protein (N) complexed with the viral RNA. The haemagglutinin esterase (HE) protein is also coded for in HuCoV-OC43 and some animal corona viruses, but not in SARS-CoV [10]. There are other ORFs (open reading frames), whose functions are being gradually revealed. Corona viruses have a unique replication system in that all mRNAs form a nested set with a common polyadenylated 3′-end, with only the unique 5′-end fragment being translated into amino acids [11]. Mutations are common, as for all RNA viruses, and if two corona viruses infect the same host cell simultaneously genetic recombination is possible [12]. However, no evidence of recombination was found from the SARS-CoV genomes detected during the course of global outbreak in 2003 [13,14].

"*A new virtual reality tool offers us a chance to "step inside" the SARS-CoV-2 virus's main enzyme responsible for replication and manipulate it in atomic detail to find ways to shut it down."*

Complications

Fever (but not always) and / or Chills

Cough

Sore throat

Runny or stuffy nose

Watery, red eyes

Body aches

Headache

Fatigue

Diarrhea

Nausea and vomiting

Loss of Smell and/or Taste

Composition of Extracts

Tinosporea corylifolia 2200 mg

Andrographis paniculata 100mg

Curcuma longa 100mg

Trikatu 100mg

(Equal part of Zingibar officinalis,

Piper longum, Piper nigrum)

Excipients: qs

Each Capsule 500 mg.

THERAPEUTIC SIGNIFICANCE OF COMPOSITION AND PATHOGENESIS OBSERVATION

To evaluate the composition of four plant extracts, 40 voluntary human clinical study had been taken.

AN AYURVEDIC PROPRIETORY MEDICINE PROVIDED free OF Cost to all Patients

1. Voluntary Pilot Case Study: POSITIVE: 20 ASYMPTOMATIC: 23

2. It is remarkable to observe and note that 90 % of the patients recovered within

3-7 days with safety and efficacy.

3. Dosage Regime: As required: 2 bid OR 2 tds Followed by Water.

4. It is noteworthy here to note that most of the patients developed either

Forgetfulness, clumsy temperament and partially Loss of Appetite.

5. All patients advised to take multi vitamin along with VIROJIT™. Other

Dietary guidelines provided.

6. Result oriented Relief in Oxidative Stress was prime focused.

7. Diabetic Patients provided 2 tds dosage regime.

8. ANY SIDE / ADVERSE EFFECTS OBSERVED: N I L

References:

. THE NEW MICROBIOLOGICA, **29**, 1-10, 2006: Functions of the HIV-1 matrix protein p17:

Simona Fiorentini, Elena Marini, Sonia Caracciolo, Arnaldo Caruso-

Department of Experimental and Applied Medicine, Section of Microbiology, University of Brescia, Italy

2**.** HIV-1 matrix protein p17 enhances the proliferative activity of natural killer cells and increases their ability to secrete Proinflammatory cytokines.

3. **Authors:** Vitale M.; Caruso A.[1]; De Francesco M.A.[1]; Rodella L.[2]; Bozzo L.[1]; Garrafa E.[1]; Grassi M.[1]; Gobbi

G.[3]; Cacchioli A. [4]; Fiorentini S.[1] **Source:** British Journal of Haematology, Volume 120, Number 2, January 2003,

pp. 337-343(7) Publishers**:** Blackwell Publishing.

4. p17 HIV-1 matrix protein: Stephen Matthews[*%], Paul Barlow[*], Jonathan Boyd[%], Geoff Barton[+], Robert Russell[+],

Helen Mills[#], Mark Cunningham[#], Nicola Meyers[#], Nigel Burns[#], Nigel Clark[*], Susan Kingsman[*], Alan Kingsman[*]

and Iain Campbell[*%]: Department of Biochemistry, University of Oxford, Oxford OX1 3QU, UK. + Laboratory of

Molecular Biophysics, University of Oxford, Oxford OX1 3QU, UK. # British Biotechnology Ltd, Watlington

Road, Oxford OX4 5LY Oxford Centre for Molecular Sciences, University of Oxford, Oxford OX1 3QU, UK.

5. Human antibody to matrix protein (p17) neutralizes HIV in vitro: Kageyama S, Ismail S, Katsumoto T, Hossain M,

Gao M,Taniguchi K, Sasao F, Toya M, Wakamiya N, Tsuchie H. – *Int. Conf AIDS.*

1994, Aug 7-12; 10: 86 (abstract no. PA0224). Dept. Pathol. Res. Inst. for Microbial Dis., Osaka Univ., Suita,

Japan.

6. The affinity of IgG antibodies to gag p24 and p17 in HIV-1-infected patients correlates with disease progression

D Chargelegue, C M Stanley, C M O'Toole, B T Colvin, and M W Steward London Hospital Medical College, UK.

7. p24 *(HIV):* A major core protein of the human immunodeficiency virus encoded by the HIV gag gene. HIV- seropositive individuals mount a significant immune response to p24 and thus detection of antibodies to p24 is one basis for determining HIV infection by ELISA and Western blot assays. The protein is also being investigated as a potential HIV immunogen in vaccines.Mallam Nock Joshua[1], Qi Yipeng, Huang Yongxiu[1] and Liu Ziye' 1 August 1997.

8. Clinical assessment of Anti HIV Drug: Bioactive Composition focused on various glycoproteins – p17, p24, p31, p41, p51/55, p66, p120, p160. – ***Shukla M.H., India, 1986-2013.***

1. Ammon HPT, Wahl MA. Pharmacology of Curcuma longa. *Planta Medica*. 1991;57(1):1–7. [PubMed] [Google Scholar]

2. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Research*. 2003;23(1 A):363–398. [PubMed] [Google Scholar]

3. Sharma RA, Gescher AJ, Steward WP. Curcumin: the story so far. *European Journal of Cancer*. 2005;41(13):1955–1968. [PubMed] [Google Scholar]

4. Jovanovic SV, Boone CW, Steenken S, Trinoga M, Kaskey RB. How curcumin works preferentially with water soluble antioxidants. *Journal of the American Chemical Society*. 2001;123(13):3064–3068. [PubMed] [Google Scholar]

5. Wang Y-J, Pan M-H, Cheng A-L, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. *Journal of Pharmaceutical and Biomedical Analysis*. 1997;15(12):1867–1876. [PubMed] [Google Scholar]

6. Huang M-T, Ma N, Lu Y-P, et al. Effects of curcumin, demethoxycurcumin, bisdemethoxycurcumin and tetrahydrocurcumin on 12-*O*-tetradecanoylphorbol-13-acetate-induced tumor promotion. *Carcinogenesis*. 1995;16(10):2493–2497. [PubMed] [Google Scholar]

7. Wahlstrom B, Blennow G. A study on the fate of curcumin in the rat. *Acta Pharmacologica et Toxicologica*. 1978;43(2):86–92. [PubMed] [Google Scholar]

8. Ravindranath V, Chandrasekhara N. Absorption and tissue distribution of curcumin in rats. *Toxicology*. 1980;16(3):259–265. [PubMed] [Google Scholar]

9. Ravindranath V, Chandrasekhara N. In vitro studies on the intestinal absorption of curcumin in rats. *Toxicology*. 1981;20(2-3):251–257. [PubMed] [Google Scholar]

10. Holder GM, Plummer JL, Ryan AJ. The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. *Xenobiotica*. 1978;8(12):761–768. [PubMed] [Google Scholar]

11. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PSSR. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Medica*. 1998;64(4):353–356. [PubMed] [Google Scholar]

12. Chen A-L, Hsu C-H, Lin J-K, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Research*. 2001;21(4 B):2895–2900. [PubMed] [Google Scholar]

13. Sharma RA, McLelland HR, Hill KA, et al. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical Cancer Research*. 2001;7(7):1894–1900. [PubMed] [Google Scholar]

14. Sharma RA, Euden SA, Platton SL, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clinical Cancer Research*. 2004;10(20):6847–6854. [PubMed] [Google Scholar]

15. Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. *Annals of the New York Academy of Sciences*. 2005;1056:206–217. [PubMed] [Google Scholar]

16. Huang M-T, Lou Y-R, Ma W, Newmark HL, Reuhl KR, Conney AH. Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice. *Cancer Research*. 1994;54(22):5841–5847. [PubMed] [Google Scholar]

17. Mohandas KM, Desai DC. Epidemiology of digestive tract cancers in India. V. Large and small bowel. *Indian Journal of Gastroenterology*. 1999;18(3):118–121. [PubMed] [Google Scholar]

18. Sidhu GS, Singh AK, Thaloor D, et al. Enhancement of wound healing by curcumin in animals. *Wound Repair and Regeneration*. 1998;6(2):167–177. [PubMed] [Google Scholar]

19. Folkman J, Shing Y. Angiogenesis. *The Journal of Biological Chemistry*. 1992;267(16):10931–10934. [PubMed] [Google Scholar]

20. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nature Medicine*. 1995;1(1):27–31. [PubMed] [Google Scholar]

21. Thaloor D, Singh AK, Sidhu GS, Prasad PV, Kleinman HK, Maheshwari RK. Inhibition of angiogenic differentiation of human umbilical vein endothelial cells by curcumin. *Cell Growth and Differentiation*. 1998;9(4):305–312. [PubMed] [Google Scholar]

22. Arbiser JL, Klauber N, Rohan R, et al. Curcumin is an in vivo inhibitor of angiogenesis. *Molecular Medicine*. 1998;4(6):376–383. [PMC free article] [PubMed] [Google Scholar]

23. Toda S, Miyase T, Arichi H, Tanizawa H, Takino Y. Natural antioxidants. III. Antioxidative components isolated from rhizome of Curcuma longa L. *Chemical and Pharmaceutical Bulletin*. 1985;33(4):1725–1728. [PubMed] [Google Scholar]

24. Gaddipati JP, Sundar SV, Calemine J, Seth P, Sidhu GS, Maheshwari RK. Differential regulation of cytokines and transcription factors in liver by curcumin following hemorrhage/resuscitation. *Shock*. 2003;19(2):150–156. [PubMed] [Google Scholar]

25. Deodhar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane) *The Indian Journal of Medical Research*. 1980;71:632–634. [PubMed] [Google Scholar]

26. Lal B, Kapoor AK, Agrawal PK, Asthana OP, Srimal RC. Role of curcumin in idiopathic inflammatory orbital pseudotumours. *Phytotherapy Research*. 2000;14(6):443–447. [PubMed] [Google Scholar]

27. Lal B, Kapoor AK, Asthana OP, et al. Efficacy of curcumin in the management of chronic anterior uveitis. *Phytotherapy Research*. 1999;13(4):318–322. [PubMed] [Google Scholar]

28. Satoskar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. *International Journal of Clinical Pharmacology, Therapy, and Toxicology*. 1986;24(12):651–654. [PubMed] [Google Scholar]

29. Srimal RC, Dhawan BN. Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. *The Journal of Pharmacy and Pharmacology*. 1973;25(6):447–452. [PubMed] [Google Scholar]

30. Siddiqui AM, Cui X, Wu R, et al. The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-γ . *Critical Care Medicine*. 2006;34(7):1874–1882. [PubMed] [Google Scholar]

31. Forman BM, Chen J, Evans RM. The peroxisome proliferator-activated receptors: ligands and activators. *Annals of the New York Academy of Sciences*. 1996;804(1):266–275. [PubMed] [Google Scholar]

32. Zingarelli B, Sheehan M, Hake PW, O'Connor M, Denenberg A, Cook JA. Peroxisome proliferator activator receptor-gamma ligands, 15-deoxy-Delta(12,14)-prostaglandin J2 and ciglitazone, reduce systemic inflammation in polymicrobial sepsisby modulation of signal transduction pathways. *Journal of Immunology*. 2003;171(12):6827–6837. [PubMed] [Google Scholar]

33. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. *Nature*. 1998;391(6662):79–82. [PubMed] [Google Scholar]

34. Jiang C, Ting AT, Seed B. PPAR-γ agonists inhibit production of monocyte inflammatory cytokines. *Nature*. 1998;391(6662):82–86. [PubMed] [Google Scholar]

35. Chen F, Wang M, O'Connor JP, He M, Tripathi T, Harrison LE. Phosphorylation of PPARγ via active ERK1/2 leads to its physical association with p65 and inhibition of NF-κβ . *Journal of Cellular*

Biochemistry. 2003;90(4):732–744. [PubMed] [Google Scholar]

36. Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-*κβ*-regulated gene products. *Cancer Research*. 2007;67(8):3853–3861. [PubMed] [Google Scholar]

37. Jagetia GC, Aggarwal BB. "Spicing up" of the immune system by curcumin. *Journal of Clinical Immunology*. 2007;27(1):19–35. [PubMed] [Google Scholar]

38. Hu M, Du Q, Vancurova I, et al. Proapoptotic effect of curcumin on human neutrophils: activation of the p38 mitogen-activated protein kinase pathway. *Critical Care Medicine*. 2005;33(11):2571–2578. [PubMed] [Google Scholar]

39. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*. 2001;29(7):1303–1310. [PubMed] [Google Scholar]

40. Ayala A, Chung C-S, Lomas JL, et al. Shock-induced neutrophil mediated priming for acute lung injury in mice: divergent effects of TLR-4 and TLR-4/FasL deficiency. *American Journal of Pathology*. 2002;161(6):2283–2294. [PMC free article] [PubMed] [Google Scholar]

41. Taneja R, Parodo J, Jia SH, Kapus A, Rotstein OD, Marshall JC. Delayed neutrophil apoptosis in sepsis is associated with maintenance of mitochondrial transmembrane potential and reduced caspase-9 activity. *Critical Care Medicine*. 2004;32(7):1460–1469. [PubMed] [Google Scholar]

42. Collin M, Patel NS, Dugo L, Thiemermann C. Role of peroxisome proliferator-activated receptor-*γ* in the protection afforded by 15-deoxy$\Delta^{12,14}$ prostaglandin J2 against the multiple organ failure caused by endotoxin. *Critical Care Medicine*. 2004;32(3):826–831. [PubMed] [Google Scholar]

43. Abdelrahman M, Sivarajah A, Thiemermann C. Beneficial effects of PPAR-*γ* ligands in ischemia-reperfusion injury, inflammation and shock. *Cardiovascular Research*. 2005;65(4):772–781. [PubMed] [Google Scholar]

44. Abdelrahman M, Collin M, Thiemermann C. The peroxisome proliferator-activated receptor-*γ* ligand 15-deoxy$\Delta^{12,14}$ prostaglandin J2 reduces the organ injury in hemorrhagic shock. *Shock*. 2004;22(6):555– Channappanavar, R., Fehr, A. R., Vijay, R., Mack, M., Zhao, J., Meyerholz, D. K., et al. (2016). Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe* 19, 181–193. doi: 10.1016/j.chom.2016.01.007PubMed Abstract | CrossRef Full Text | Google ScholarChannappanavar, R., and Perlman, S. (2017). "Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin. Immunopathol.* 39, 529–539. doi: 10.1007/s00281-017-0629-x

ACKNOWLEGEMENT:

I am indebted to my wife Harsha Shukla for financing the project. I am also grateful to my daughters Sejal Raval and Kunjal Acharya for dedicating time to prepare the project profile. I am highly obliged to Dr.Ajay Padmawar for the invaluable guidance in formulation and preparation of significant chemistry of the drug.