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A NEW DIRECTION TO COMBAT A GLOBAL PANDEMIC CORONA VIRUS DISEASE (COVID-19) BY A BROAD SPECTRUM PROTEASE INHIBITOR – ALPHA-2-MACROGLOBULIN (A2M)

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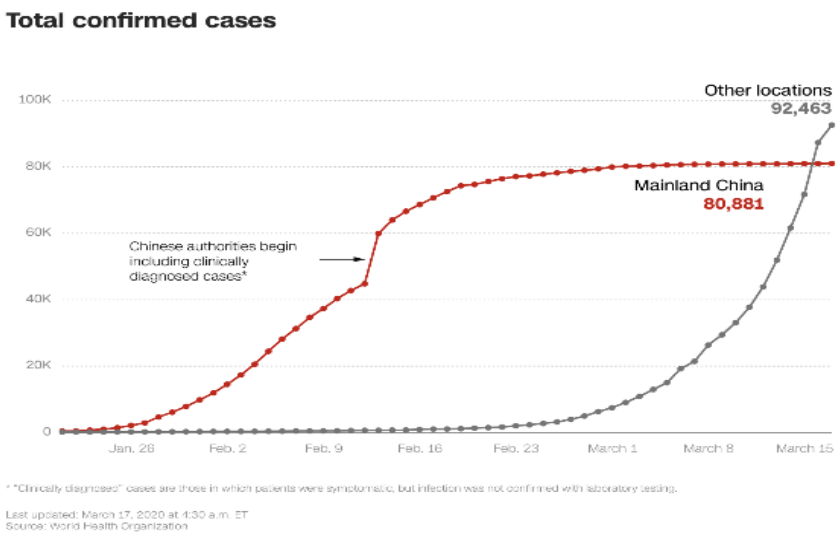
ABSTRACT

Currently a pandemic, an emerging, rapidly evolving deadly respiratory disease killing thousands of people every day in the world caused by a novel coronavirus that was first reported from Wuhan, China, on 31 December 2019 and which has now been detected in more than 100 locations internationally, including in the United States. The virus has been named "SARS-CoV-2" and the disease it causes has been named "coronavirus disease 2019" (abbreviated "COVID-19"). World Health Organization (WHO) described about COVID-19 on March 13, 2020 that "Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). A novel coronavirus (nCoV) is a new strain that has not been previously identified in humans. Coronaviruses are zoonotic, meaning they are transmitted between animals and people. Detailed investigations found that SARS-CoV was transmitted from civet cats to humans and MERS-CoV from dromedary camels to humans. Several known coronaviruses are circulating in animals that have not yet infected humans. According to the report from CNN (March 17, 2020): There is now a total of 173,334 reported cases of COVID-19 globally and 7019 deaths. In China reported 80,881 and death 3194. Most cases continue to be reported from Hubei province. Outside of China 61,518 confirmed 2199 deaths and 135 countries are affected.



Older people and those with chronic illnesses should take precautions now against the coronavirus.

According to CDC, there is no specific antiviral treatment recommended for COVID-19 yet. People with COVID-19 should receive supportive care to help relieve symptoms. For severe cases, treatment should include care to support vital organ functions.

Many pharmaceutical companies in the world are trying to stop viral entry and also viral growth in the body.

Our suggestions for the prevention and cure of covid-19

Since there is no treatment available yet, we are suggesting a new pathway to stop this lethal disease based on a recent study[1] where it was shown that at least 56 people (34-82 years) do not have any health issues for last 2-5 years (even no fever, cough or common cold).

This miracle success was possible only after using a new novel "A2M-ShopAnn System" based on several biomedical research for last 40 years to understand the mechanism of starting of disease(s) and their prevention. "A2M-ShopAnn System" is a combination of few simple daily intake of poly-phenol containing foods with some other healthy food materials (which is described later with a list of foods) and disciplined life pattern.

The main goal was to keep us healthy by maintaining a broad spectrum protease inhibitor, alpha-2-macroglobulin (A2M) in physiological concentration in our body, which in turn protects us from (almost 500) the toxic effect of free protease(s).

Background for our suggestions

The concept of protecting mechanism of A2M is based on previously published studies (supported the beneficial effect of inhibiting proteases by A2M) which are as follows.

- In 1994, we have first published a paper in which it was shown that we have created an acute intra-abdominal *Pseudomonas aeruginosa* bacteria containing fibrin-thrombin clot implanted septic shock model (guinea pigs and rats). In that study when all guinea pigs and rats were dying about 7-8 hours (after the implantation) due to septic shock, at that crisis stage, intravenous injection of purified active A2M was able to rescue all of the guinea pigs and rats from death.[3-4] That was the first report showed that it was not the endotoxin Lipopolysaccharide (LPS) but protease(s) are responsible for septic shock and only broad spectrum protease inhibitor, A2M, is the treatment for septic shock. In reference to that, around in 1994, 11 clinical trial with anti-endotoxin antibody failed completely because the cause of septic shock was not LPS (what was believed at that time). Because LPS comes from Gram negative bacterial wall only. But it was found that septic shock can be occurred with Gram positive bacteria, fungus or yeast also. It indicated that in the pathophysiology of septic shock, definitely other bacterial products are involved, not only endotoxin (LPS).

- If the same amount of LPS obtained from bacterial culture of Gram negative bacteria is injected nothing happens to animal model. In contrast, If the same amount of protease obtained from bacterial culture of Gram negative bacteria is injected all of the guinea pigs die immediately.[5,6]

- After those studies with animals we found that in the pathophysiology of multiple diseases in human various types of proteases played the key role for the cause of the disease(s).[7]

- Several interesting papers showed that, one type of rat (Naked Mole Rat-NMR) in south east Africa are resistant to cancer and they have long life (survive double the time of their same species). It was also found that plasma A2M concentration of those rats is double the amount of human A2M.[8-9] Excess amount of A2M was the reason for their cancer free long life.

To find out their food habits those are responsible for their long cancer free life with high A2M concentration, several studies were also done by their stool examinations. NMR mouse showed that they eat those kind of foods which are high polyphenol containing foods (such as clove powder, mint leaf etc. and more which are described later in the text).[9]

- We finally found that eating polyphenol containing foods with some other food items can prevent the starting of many diseases(s) and keeping us healthy.[1]

- Clinically also we found the proof to support this hypothesis that "when the A2M is less in our body to protect proteases we are vulnerable to start disease(s) by varity of different types of free proteases". The study is as follows: (Figure 1)

Randomly chosen 31 admitted patients in one of the hospitals in Bangladesh showed serum A2M level significantly went down 4 fold (from age matched controlled group). Oppositely, serum protease (trypsin) level went up almost 10 fold (from age matched controlled group).[10]

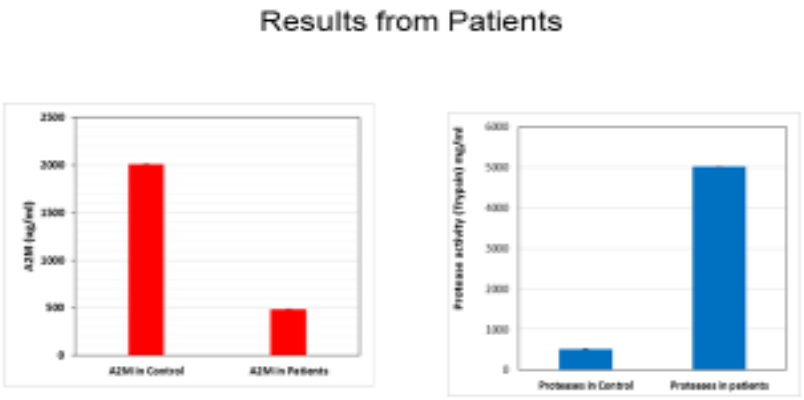


Figure 1.

The severity of the disease depends on type of protease(s), how long the protease activity was in the body and how low is A2M in the body. So there is a question of supply and demand. This means how much A2M are available in the body versus how many proteases to remove from the body. If A2M is enough to remove protease(s) then there will be no chances to start sickness since the main cause of starting of many sickness is due to protease(s) as shown before.[6,9]

- In addition to prevention of starting of any sickness, using the combination of natural foods (A2M-ShopAnn System) also prevented the complications of uncontrolled diabetes and hypercholesterolemia for more than five years.[11]

Reason to produce intact un-activated A2M naturally from liver by poly phenol containing foods

Because of the high molecular weight of un-activated A2M (720kDa), we could not use any of the methods of drug delivery system to use A2M as a medicine. On the other hand it is very important to keep physiological concentration and un-activated A2M in our body all the time to remove proteases and keep us healthy. Because if it is activated then A2M will not work to trap proteases. So far we know (Figure 3A) the activation mechanism needs protease. Protease cleave a '35 amino acid conserved a specific area' called "bait region" of A2M. After the cleavage of bait region of A2M, 2 di-sulfide bond containing linear protein pass through a conformational change and capture two molecule of proteases. The A2M-protease complex bind to the receptor on a special type of cell (macrophage) and eliminated from the body. In this way un-wanted proteases are removed from our body continuously without our knowledge and keep us healthy.[7,12]

Normally, liver generates A2M all the time to clear proteases as well as other toxic products to keep us healthy without our knowledge. Only we become sick when there is shortage of A2M. Since so far almost 500 types of proteases are available for many physiological functions, if the imbalance between A2M-protease concentration occurs, sickness followed by diseases starts. Normally we all are protected by physiological concentration of A2M all the time.[7,13]

In general, viruses express polyproteins that are precisely cleaved by the viral protease(s) during replication and particle assembly. The viral entry is determined primarily by host cellular, trypsin-type, processing proteases that proteolytically activate the fusion glycoprotein precursors of many types of viruses. At least five different processing proteases have been identified in the airways of animals and humans.[2]

Like other viruses COVID-19 also releases proteases. Viral proteases are enzymes (endopeptidases EC 3.4. 2) encoded by the genetic material (DNA or RNA) of viral pathogens. The role of these enzymes is to catalyze the cleavage of specific peptide bonds in viral polyprotein precursors or in cellular proteins.

Proteases regulate multiple biological processes including cell differentiation, proteasomal degradation, inflammation, tissue remodeling, apoptosis, cell homeostasis, and coagulation. Consequently, the deregulation of proteolytic activity accounts for pathogenesis and progression of many diseases such as cardiovascular disease, inflammatory conditions, neurodegenerative disorders and cancer.[10]

Proteases can be found in all forms of life and viruses. Proteases can be classified into seven broad groups

- Serine proteases - using a serine alcohol
- Cysteine proteases - using a cysteine thiol
- Threonine proteases - using a threonine secondary alcohol
- Aspartic proteases - using an aspartate carboxylic acid
- Glutamic proteases - using a glutamate carboxylic acid
- Metalloproteases - using a metal, usually zinc[1][2]
- Asparagine peptide lyases - using an asparagine to perform an elimination reaction (not requiring water).

Figure 2. Proteases can activate multiple different vital pathways and involved in many disease(s).[7]

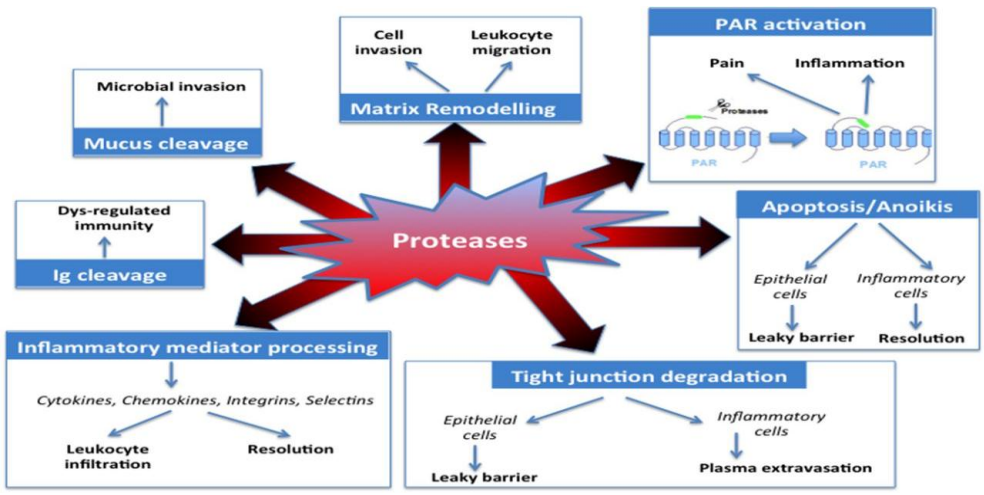


Figure 2.

CDC recommendation for the prevention from COVID-19

Since there is **NO** treatment for COVID 19 until today (March 15, 2020), the best way to prevent illness is to avoid being exposed to this virus. However, as a reminder, CDC always

recommends everyday preventive actions to help prevent the spread of respiratory diseases, including

- Wash Hands with soap and water if hands are visibly dirty
- Avoid close contact with people who are sick.
- Avoid touching your eyes, nose, and mouth.
- Stay home when you are sick.
- Cover your cough or sneeze with a tissue, then throw the tissue in the trash.
- Clean and disinfect frequently touched objects and surfaces using a regular household cleaning spray or wipe.
- Follow CDC's recommendations for using a facemask.

CDC does not recommend that people who are well wear a facemask to protect themselves from respiratory diseases, including COVID-19.

Facemasks should be used by people who show symptoms of COVID-19 to help prevent the spread of the disease to others. The use of facemasks is also crucial for health workers and people who are taking care of someone in close settings (at home or in a health care facility).

Wash your hands often with soap and water for at least 20 seconds, especially after going to the bathroom; before eating; and after blowing your nose, coughing, or sneezing.

If soap and water are not readily available, use an alcohol-based hand sanitizer with at least 60% alcohol. Always wash

We agree completely the recommendations of CDC

In addition to the recommendation of CDC, we suggest to measure not only virus itself of the suspected patients, we need to measure toxins (those are released by COVID-19), especially all types of proteases and a broad spectrum protease inhibitor: alpha-2-macroglobulin (A2M).

Proteases are enzymes, continuously secreted by micro-organisms for penetration, survival and their growth.[2] The toxic effects of proteases continue even after removal of virus or bacteria by antiviral or antibiotics respectfully. Therefore, even after negative results of viral load, patient could be sick continuously depends on amount of protease clearance by A2M.

As prophylaxis natural food items (A2M-ShopAnn System) should be started immediately to maintain physiological concentration of plasma A2M for everyone.

We showed the mechanism by which A2M forms A2M-protease complex (Figure 3 A - normal healthy situation) to understand the mechanism to stop Covid-19 toxicity and viral growth (Figure 3 B).

Flow chart to combat covid-19

COVID-19 ➡ secretes proteases ➡ proteases are captured by A2M (A2M-protease complex) ➡ eliminate proteases from body ➡ losing protease activity ➡ Loosing

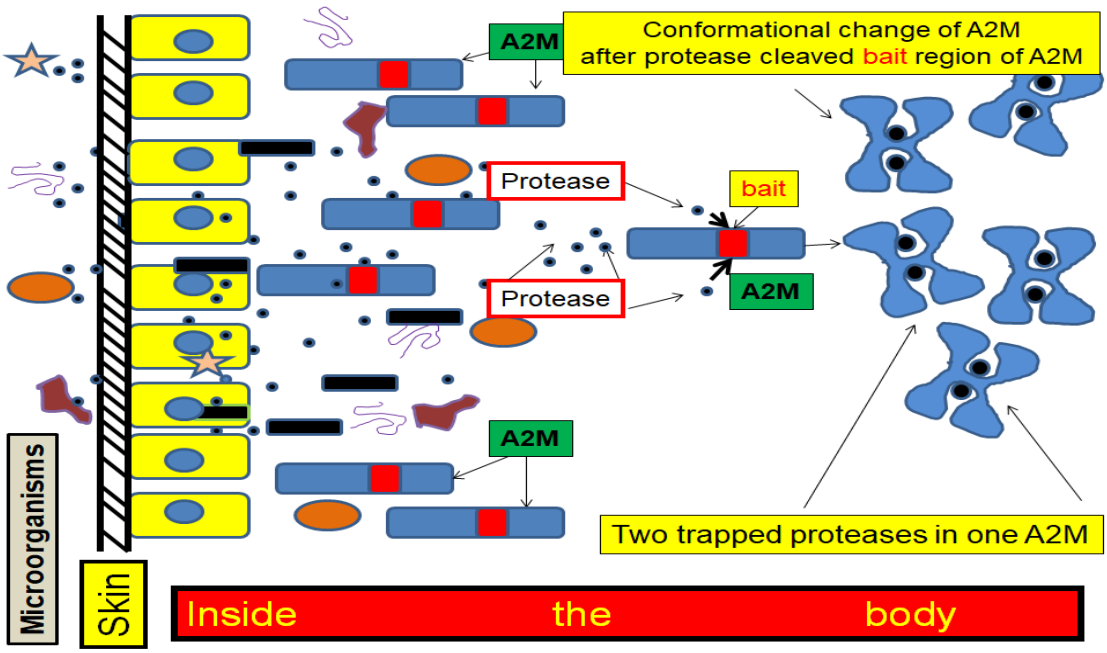


Figure 3 A. (normal healthy situation).

Schematic diagram is showing in normal physiological condition how protease(s) ( ) from different kind of microorganisms (, , ,) cleaves "bait region " " of un-activated A2M ( ) becomes activated ( ). After cleavage of bait region of A2M by protease, A2M goes into a conformational change ( ) and immediately grip two molecule of proteases ( ) and become A2M-protease complex ( ). This A2M-protease complex binds with a receptor on macrophage and macrophage-A2M-protease complex is expelled from the body by a complex mechanism of reticulo-endothelial system.[7]

Normally we are protected from protease activity by A2M and maintain our body healthy without our knowledge.

When the plasma concentration of A2M become low, unwrapped free protease concentration gradually starting to go high and toxic effect of free protease starting to activate multiple defense as well as other systems that start to make us sick. Depending of plasma A2M concentration, activation of multiple systems such as coagulation, fibrinolytic, complement, intraleukin (IL), thrombin receptor activated protease (TRAP), matrix metallo protease (MMP) etc. are activated. Since the homeostasis in the body is broken down, multi organ failure starts which may end to the tragic death.[7,13]

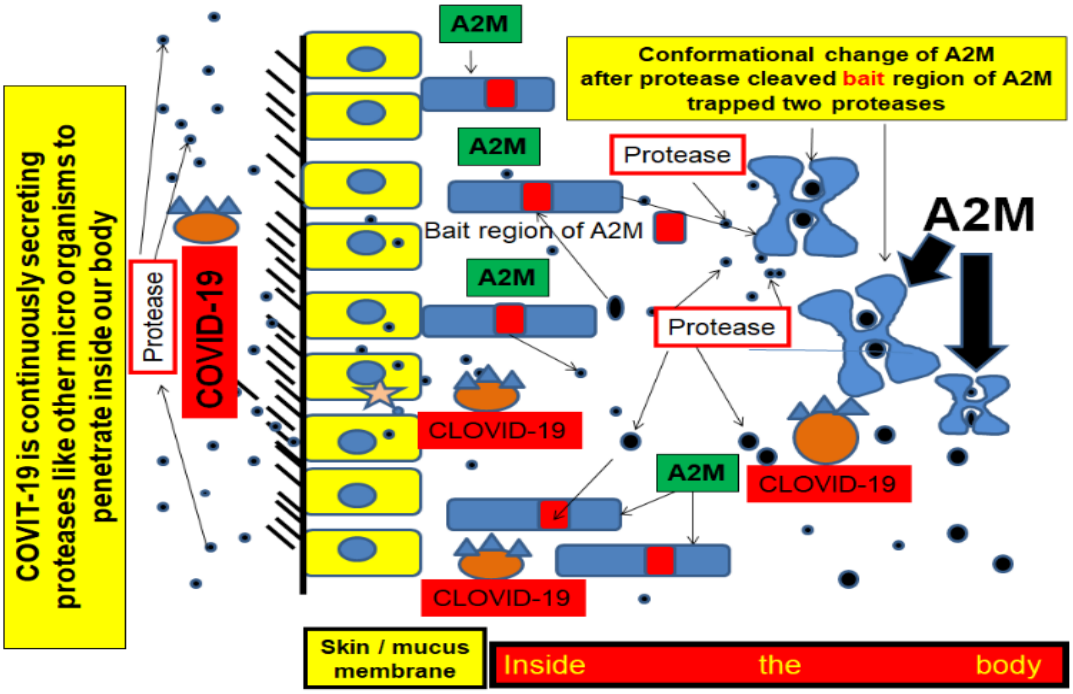


Figure 3: B. (proposed mechanism by which A2M can inhibit proteases secreted by COVIT-19 and combat viral growth).

Like other microorganisms, COVID-19 ( ) also secretes proteases ( ) for its penetration, toxicity and growth inside the body. We propose the same mechanism (described in Figure 3 A) by which the toxicity and growth of COVIT-19 could be treated with active native A2M.

In the catastrophic sequence of COVID-19 infection, A2M could be generated from liver with the stimulation of simple polyphenol containing food materials (A2M-ShopAnn System).

Virulence and toxicity depends on the clearance of the proteases by A2M. Therefore, with the measuring of viral load, proteases and A2M are also essential to measure in suspected and sick cases.

Suggested method of raising plasma A2M in the body[1]

Selected few items from 40 polyphenol containing foods: published before[1]

Herbs and Spices High in Polyphenols (mg)

1. Cloves (15,188 mg per 100 g)
2. Peppermint, Dried (11,960 mg per 100 g)

Fruits High in Polyphenols

1. Black Chokeberry (1,756 mg per 100 g)
2. Black Elderberry (1,359 mg per 100 g)
3. Lowbush Blueberry (836 mg per 100 g)
4. Blackcurrant (758 mg per 100 g)
5. Highbush Blueberry (560 mg per 100g)
6. Plum (377 mg per 100g)

Some other food items (healthy foods)[1]

Raw garlic - chopped finely (2 cloves), Raw ginger - chopped finely - 1 teaspoon, Raw (bitter melon –Karella) juice - 5 teaspoons, Rose apple juice - 5 teaspoons, Black cumin – 2 teaspoons, Raw turmeric juice - 2 teaspoons, Extra virgin olive Oil - 1 tablespoon, Basil (Tulsi) juice - 2 teaspoons, Fenugreek (Methi) - 1 tablespoon, Date - 1 piece, Grapes – 5, Variety of green vegetables - Half kg, Honey - Half teaspoon, Milk – 1 glass, Ripe banana – 1 piece, Cinnamon powder – ½ teaspoon, Watermelon drink - 1 glass + honey – 1 teaspoon + Lemon juice - 1 teaspoon, Pomegranate – 1/2 cup, Fish or meat - 1 cup, Figs -1, Egg-1, Yogurt- 1 cup, Water – 3 liters (in 24 hours)

Currently there are many anti-proteases treatment are available to treat many diseases (Table 1). For example, in HIV treatment anti-retroviral drugs are used (atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), indinavir (Crixivan), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase) (Figure 5 A).

All of these are against only one type of protease (Aspartic protease) (Figure 5 A). It is not known yet how many types of proteases are generated from Corona viruses. Therefore we

need a broad spectrum protease inhibitor (A2M) to inhibit all kind of proteases (Figure 5 B) secreted from Corona virus.

In table 1, it is shown that in how many diseases protease inhibitors are being used.[7]

Table 1: Protease inhibitors are used as drugs in many diseases.

Serine protease inhibitors in clinic			
Protease	**Function**	**Disease**	**Drug/Status**
Thrombin	Blood coagulation	Stroke	Argtroban, bivalirudin
		Coronary infarction	Ximelagartan, Melagatran
Factor Xa	Blood coagulation		Danaparoid (launched),
			DX-9065a, CI-1031(Phase-II trial)
			DPC-906, JTV-803(Phase-II trial)
			MLN-1021,PMD-3112(Phase-I trial)
Factor VIIa			NAPc2 (Phase-I trial)
HNE elastase	Cleaves elastin	SIRS	Sivelestat (Japan only)
		ARDS	Sivelestat (Phase-II trial, USA)
Complement	Inhibition	Inflammation	Nafamostat, FUT-175
HCV	HCV repication	Hepatitic C	BLIN-2061 (Phase-II trial)
			VX-950(Preclinical)
PAI (Urokinase)		Cancer	WX U K1 (Phase II)
			Aminocaproic Acid (Phase III)
		Ulcer, Psoriasis	PAI-2 (Phase-II trial)
Matriptase		Prostate Cancer	CVS-3983
Chymase	Restenosis		NK-3201 (preclinical)
Dipeptydil Peptidase IV		Diabetes type II	LAF-237, P32/98 (Phase-II trial)
Aspartic protease inhibitors in clinic			
Protease	**Function**	**Disease**	**Drug/Status**
HIV-1 protease	HIV replication	HIV/AIDS	Indinavir, Nelfinavir,
			Amprinavir, Ritonavir,
			Lopinavir, Saquinavir,
			Atazanavir, Fosamprenavir.
			Tipranavir (Phase III)
			(monotherapy unsuccessful)
Renin	forms Angiotensin 1	Hypertension	Aliskiren (Phase II)
BASE	forms Ab_4	Alzheimers	Elan (Preclinical)
			Actelion (Preclinical)
			Locus (Preclinical)
			TGCN-001(Preclinical)
			Astex Technology (Preclinical)

			Sunesi s (Preclinical)
			De Novo (Preclinical)
Cysteine protease inhibitors in clinic			
Protease	**Function**	**Disease**	**Drug/Status**
Rhinovirus	Viral replication	SARS	Ruprintrivir(preclinical)
SARS CoV M	Viral replication	SARS	AG7088(preclinical)
Cathepsin K	Bone resorption	Osteoporesis	AEE-58,SB-462795(Phase-II)
Caspase 1	Cytokinine release	Arthritis	VX-765 (Phase-1)
			Pralnacasan (phase II)
Caspase 3	Apoptosis	Cancer, Alzhemier	Locus Pharma
		Ischaemia, Sepsis	Novartis (preclinical)
Caspase 8	Apoptosis	Sepsis, Diabetes	IDN-6556 (Phase II)
Cruzain	parasitic replication	Trypanosomiasis	K-777, INPL-022-E7 (preclinical)
Cathepsin F, L, S			INPL-022-E7, D6 (preclinical)
Metallo protease inhibitors in clinic			
Protease	**Function**	**Disease**	**Drug/Status**
ACE-1	Forms Angiotensin-II	Hypertension	Trandolapril, Enalapril, Captopril
NEP	Release of ANP	Hypertension	Candroxatril (discontinued)
TACE	Release of TNFa	Arthritis, MS	BMS-561392 (Phase-II)
MMP-1	Degrades matrix	Cancer	Marimistat(discontinued),
			Neovastat (Phase-III)
		Periodontitis	Periostat
MMP-2		Cancer	Rebimistat(Phase-1)
MMP-8		Osteoarthritis	Glocosamine sulphate
MMP-9		Inflammation	Rega-3G12, Biopharma
MMP-3,13			Pfizer, Novartis (preclinical)
Threonine protease inhibitors in clinic			
Protease	**Function**	**Disease**	**Drug/Status**
Proteosome		Ischaemia	Bortezomib, MLN-519 (Phasel

Recently, in Coronavirus treatment with HIV Protease Inhibitors were suggested. Protease inhibitor drugs that are approved by the Food and Drug Administration (FDA) to treat HIV include: atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), indinavir (Crixivan), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase). All of these are against only one type of protease (ASPARTIC PROTEASE).

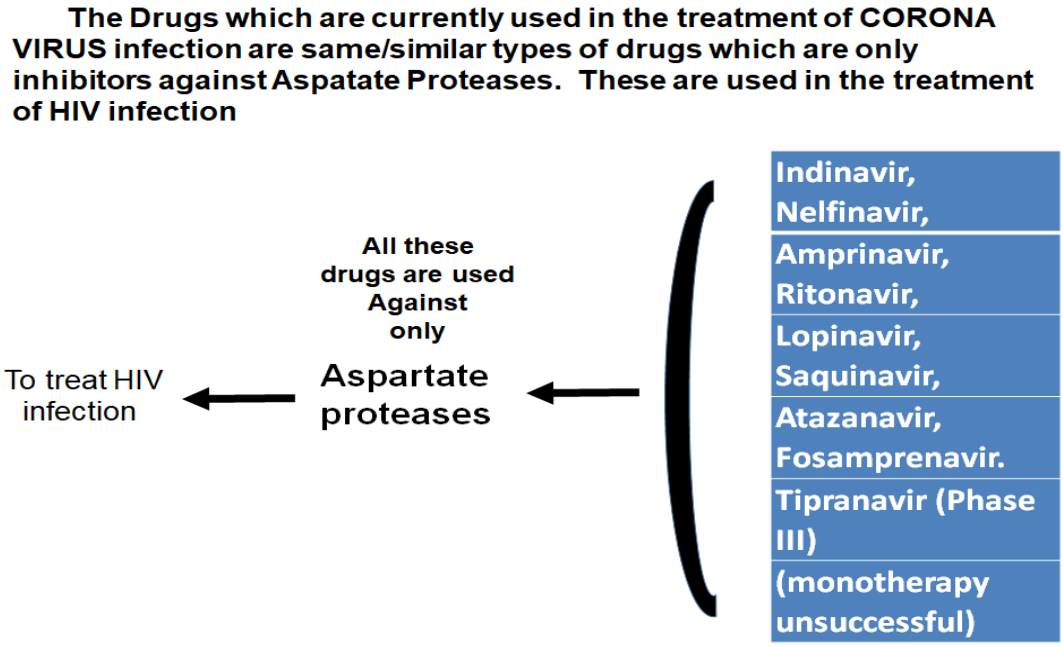


Figure 5 A.

A2M is a broad spectrum protease inhibitor. Any type of protease will be inhibited by A2M. As shown in Figure 5 B, A2M Is capable to inhibit all types of proteases.

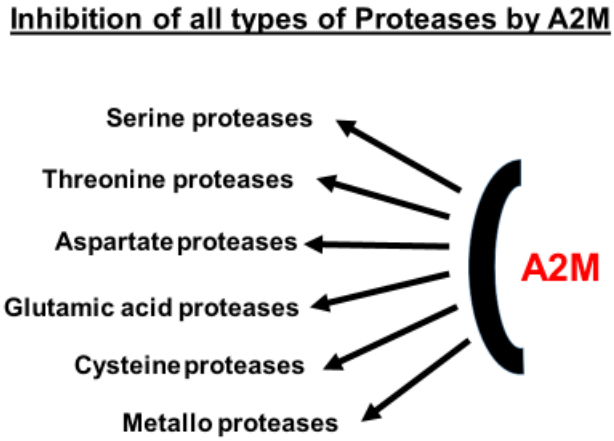


Figure 5 B.

CONCLUSION

A2M is a broad spectrum protease inhibitor in plasma, an extraordinary multifunctional blood protein, inhibits and clears many types of proteases as well as several growth factors and cytokines, including TNF-α, IL-1β, IL-6 and TGF-β from the body[7,13] had never been given any attention for a possibility as a life -saving therapeutic molecule in the field of medicine.

To protect from adverse environment and for survival, all living creatures were born with innate immune system. Microorganism invasion, metabolism and virulence are dependent on protease(s) which are secreted by prokaryotic and eukaryotic microorganism.[13-15]

A2M is a plasma protein that trap proteases and acts as a major components of the innate immune system by inhibiting a broad range of proteases.[13,16] A2M provide immediate defense against infection, and is an evolutionarily older defense strategy, found in plants, fungi, insects, bacteria and primitive multi-cellular organisms.[14]

Maintenance of plasma A2M concentration in physiological concentration is very essential for the prevention of many disease(s) including COVIT-19.

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