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Chapter 10

HISTORICAL DEVELOPMENT OF UNCARIA PREPARATIONS AND THEIR RELATED BIOACTIVE COMPONENTS

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1. OVERVIEW OF UNCARIA SP. BARK AND ITS COMMERCIAL PREPARATIONS AS A MEDICINAL HERB. THE OXINDOLE ALKALOID /WATER EXTRACTION REFERENCE STANDARD STORY

Uncaria sp. is a well known herbal medicine used for generations by the Ashinka Indians native to the Amazon basin. There have been two set of bioactive ingredients for which Uncaria extracts have been developed and standardized. The first are oxindole alkaloids, initially studied and described in 1967; the second are a set of molecules know as Carboxy Alkyl Esters (CAEs ™) first identified and described in 1997 as the bioactive ingredients in AC-11® (formerly C-MED-100®). More recently (2005) it was shown that one of the acid moieties of CAEs is quinic acid. Chlorogenic acid also is present in Uncaria sp. water extracts, where it occurs as a natural ester of quinic acid. Oxindole alkaloids are much less soluble in water than quinic acid or chlorogenic acid; hence, they are absent (<0.05%) from AC-11®, which instead contains specifically CAEs. This overview concentrates on characterization of the AC-11® water extract because it is the only Uncaria extract standardized to a bioactive chemotype that enhances DNA repair, this chemotype, is not known to be present in Uncaria sp. extracts that are latent with oxindole alkaloids.

The overview herein includes mode of action studies, as well as clinical effects, some of which are common both to water insoluble products such as oxindole alkaloids and to water soluble products such as CAEs. Examples include: anti-inflammation, nuclear fraction kappa

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beta (NF-kB) inhibition, and immune enhancement. The salient characteristic that differentiates between insoluble alkaloid based Uncaria products and water soluble CAE's, specific to AC-11 and DNA Repair enhancement, is in the nature of the bio-efficacy of each. Principally AC-11® , Uncaria tomentosa water extract, has been documented to: (i) increase serum protein thiols (antioxidant protection), (ii) increase urinary nicotinamide and tryptophan levels, (iii) increase the number of white blood cells(WBC), (iv) increase pneumococcal titer, (v) enhance DNA repair, (vi) increase lymphocyte growth response, (vii) reduce level of 8-OH quanine DNA adducts, (viii) associated to weight loss, (ix) reduce sunburn, (x) increase removal of UV-induced thymine T-T dimer DNA damage, (xi) improve life style-induced clinical responses, (xii) inhibit tumor cell growth and (xiii) inhibit inflammation; additionally other Uncaria water extracts exhibited the ability to (xiv) inhibit amyloid body formation related to Alzheimers, (xv) protect against ozone injury. (Castillo 2005,2006, Cisneros et al 2005, Lamm et al 2001, Mammone et al 2006, Miller et al 2005, Piscoya et al 2001, Pero et al 2002, 2005, 2009, Pero and Lund 2009, Sheng et al 1998, 2000A,200B, 2001, Akesson et al 2003A, 2003B, and also as cited elsewhere in this review).

2. HISTORICAL BACKGROUND

Uncaria tomentosa species has had a long history of use as a folk medicine among the indigenous peoples of Central and South America. Traditional practice was to steep the bark and stems or leaves (1-3 gm) with boiling water for several hours, and then decant the resulting "tea" and drink 1-3 cups per day. According to anecdotal evidence, preparations of this type were believed to be especially useful from a historical perspective to treat a multitude of health problems associated with rheumatism, arthritis, gastric ulcers, gastrointestinal/inflammatory/autoimmune disorders, tumors, child birth trauma, psychotropic responses (mental state) and infections. (Blumenthal, M. 2003, Capasso, F. et al 2003). Historically, most commercially produced water extracts were roughly equivalent to what is produced by the original "folk medicine" methods described above; such preparations were not further chemically altered except by what might be caused from spray drying , freeze drying or molecular sieving.

The literature documents how commercially available forms of alkaloid-based Uncaria sp. extracts are prepared. Over 50 bioactive ingredients have been identified and isolated from Uncaria sp., more than any other South American plant, since the early 1960's when Klaus Keplinger, Wagner and colleagues identified the oxindole alkaloids present in this plant (Keplinger 1982, Keplinger et al 1999, Wagner et al 1985, Stuppner et al 1992). For example, quinovic acid glycosides (Aquino et al 1989), polyhydroxylated triterpines (Aquino et al 1991), steroids (Senatore et al 1989), procyanidins (Wirth and Wagner 1992) and tannins (Jones 1995) have all been identified over the years since Keplinger, as bioactive components of Uncaria sp. extracts. Although biological properties associated with Uncaria sp. were found to exist, no one prior to 1998 was able to explain completely the apparent efficacy of these alkaloid based extracts when examined against the anecdotal record of the water extracts used by indigenous peoples in South America. Instead there was a general acceptance, with limited data, that oxindole alkaloids were responsible for the efficacious properties of Uncaria sp.

The folk medicine practice uses hot water extraction, because it was the only available method of preparation known to native Indians. This fact was ignored by Keplinger and others. Instead they used alcohol based extracts which became more common in recent decades. Therefore alcohol based solvents were used to extract the oxindole alkaloids, which were the first class of bioactives isolated from Uncaria. There are at least 17 indole alkaloids identified. Their content in plant extracts is greatly enhanced by organic solvent extraction such as with alcohol, ethyl acetate or other organic solvents, or by acidic extraction, because alkaloids are basic and they can easily be converted to salts. Nevertheless, these types of Uncaria sp. ingredients are difficult to reconcile as explanations for the historic medicinal use of Uncaria sp. based simply on their poor water solubility, thus severely limiting their presence in water extracts.

Although the resultant doses of crude Uncaria sp. extracts based on plant part concentration are more or less consistent with those produced by "folk medicine" practices, the commercially made forms vary considerable in their preparation processes. (Blumenthal 2003, Laus 2004, Montoro et al 2004, Piscoya et al 2001, Sheng et al 2000A). Doses and applications described include: (i) Teas: One to 25 grams of root bark added to 250 milliliters of pH adjusted water, boiled for five to 10 minutes, then cooled and strained. One cup taken three times daily. (ii) Water Extracts: 100-700 mg/day; such as AC-11®. (iii) Alkaloid Extracts: An extract containing only pentacyclic oxindole alkaloids taken by mouth in a dose of 20 milligrams two or three times daily for the first 10 days and then 20 milligrams thereafter. Also, 1% to 7% oxindole alkaloids extracts have been used between 100 mgs and 1000 mgs daily. (iv) Tinctures: One to two milliliters taken orally two to three times daily, or 20 to 40 drops five times daily. (v) Decoctions: One tablespoon of pulverized root in one quart of hot water taken orally before breakfast.

Early research posited a theory that 2 different types of Uncaria sp. alkaloids (i.e.chemotypes) are contained in this plant: the "bad" ones, or *tetracyclic* oxindole alkaloids (TOA's) and the 'good' ones, or *pentacyclic oxindole* alkaloids (POA's) (Montoro et al 2004; Laus et al 1997). An inconclusive investigation was made into whether the "bad" alkaloids counteracted the immune benefits of the "good" alkaloids; the presence of TOA's together with POA's appear to be immune-suppressive. Either way, there was little doubt that POA's and TOA's differ considerably in their water solubility. This was thought to be a factor of significance of how the alkaloids interact with the body. POA's moreover were shown to be concentrated more in the roots and bark of the plant, whereas, TOAs were found to be located primarily in leaves and bark. As a result of the early research, it was theorized that either organic solvent extracts of Uncaria sp. should be abandoned as chemotypes for Uncaria sp. alkaloids, or else the TOA's should be separated from the POA's by water solubility criteria, or by plant part location or both.

3. THE WATER EXTRACT METHOD

The oxindole alkaloid research was a pioneer scientific effort because it attempted to standardize the numerous bioactive indole alkaloids in Uncaria. However, in general, this class of alkaloids lacks water solubility. In addition, it is difficult to correlate the notion that these water insoluble components constitute the natural occurring active ingredients of

Uncaria sp. with field observations of how the aqueous form of the Uncaria extract was traditionally prepared in SA in use as a "folk medicine".

Accordingly, Pero and colleagues choose to focus their studies on the efficacy of water extracts or Uncaria prepared in a manner similar to the method used by the indigenous population of the Amazon Rainforest. Specifically, they did not rely on alcohol- based (i.e. organic solvent) extraction or concentration methods but sought in essence to duplicate, in a standardized setting, the "Amazon Recipe". The resulting aqueous extract first introduced by Pero was called C-MED-100®. The trade name was later changed to AC-11®. When C-Med-100®/AC-11® extract and other water-based extracts of Uncaria sp. were analyzed for oxindole alkaloids only trace amounts were found (Kuras et al 2009) Sheng et al 2000B, Sandoval et al 2002). Furthermore, it was shown through a series of scientific studies from 1998 through 2009 that CAE's, the active ingredient in C-MED-100/AC-11, were responsible for the efficacy related to enhanced DNA Repair.

Currently, only two classes of active ingredients serve as the basis for standardizing the biological activity of Uncaria sp. extracts. The first ingredients, beginning in the 1960's, were the oxindole alkaloids already cited. These ingredients were standardized as tetracyclic oxindole alkaloids (TOAs), pentacyclic oxindole alkaloids (POAs) or combinations thereof at about 1.3% POAs - 2.96 % (i.e. for all oxindole alkaloids) of the acidic or organic solvent Uncaria extracts (Blumenthal 2003, Laus et al 1999). The second class of ingredients, beginning in 1998 (Sheng et al 1998), consists of Carboxy alkyl Esters (CAEs), which are found in abundance up to 8-10 % in the water soluble AC-11® extract. AC-11® has only traces of alkaloids present (< 0.05% POAs + TOAs) (Sheng et al 2000B, 2005).

The importance of using water extracts of Uncaria products lies in the fact that the water soluble efficacious components of Uncaria are more readily available for uptake, distribution and cellular modulation. This view is confirmed by several laboratories that have used water soluble extracts of either Unacria tomentosa or Uncaria quianensis, a sub-species of Uncaria (Sandoval et at 2000, Kuras et al 2009). Another commercially available water extract of Uncaria quianensis, called Vincaria has been used as an anti-inflammatory treatment, and also reported to contain reduced oxindole alkaloids (Miller et al 2005, Piscoya et al 2001).

Detailed chemical analyses of organic solvent extractions of Uncaria sp. using sophisticated HPLC-ES/MS analyses have determined POA's to be 26.895 mg/gm and TOAs to be 2.753 mg/gm. Added together the total alkaloid content on average would be 29.649 mg/gm (Montoro et al 2004). POA's and POA content has normally been determined and identified by HPLC, whereas CAE content has been validated by a colorimetric procedure involving conversion of CAE to hydroxamic acids and reaction with ferric chloride (Bartos 1980, Sheng et al 2005). When these alkaloid concentrations are compared with the alkaloid levels shown in AC-11® or Vincaria water extracts which were < 0.05 mg/gm, or about 593 times less alkaloid content than in solvent based extracts (i.e. 29.649/ 0.05 = 593). Therefore it follows the potent anti-inflammatory properties of Uncaria sp. water extracts cannot be reasonably explained by their oxindole alkaloid content, but rather must be due to other components perhaps not found in organic solvent extracted Uncaria products. It was determined by Pero and colleagues (Sheng et al 2005) after identification and isolation of CAE's in 2000 that the CAE's were responsible for approximately 90 percent of the biological activity found in C-MED-100/AC-11. This

conclusion was validated by the charcoal filtration (removal) of CAE's at 190-200nm and the subsequent decrease in biological activity.

The alkyl group and the carboxy group in ester linkage in CAEs together have now been identified as the active ingredients in water soluble Uncaria products. Further, they have been isolated as esters of quinic acid (i.e QAEs, Sheng et al 2005). Due to the strong acidity of the stomach ($P^H = 1$), and combined with the fact that gastrointestinal microflora are efficient at metabolizing QAEs such as chlorogenic acid (Olthof et al 2003; Gonthier et al 2003), it is believed that these ingredients would be hydrolyzed to free quinic acid and the alcohol moieties for systemic uptake and absorption. It is clear from the data presented by Sheng and colleagues (Sheng et al 2005) that quinic acid is one of the bioactive components of Uncaria tomentosa and can account for about 40% of the DNA repair enhancement observed from AC-11® in vivo (Table 4 in Sheng et al 2005). This study focused on Doxorubicin-induced leucopenia in the rat model treated with 80 mg/kg of AC-11®, and measured by direct comparison to quinic acid or Quinmax™ treated with 200 mg/kg, found similar results in relationship to enhanced DNA repair capacity. Since the alcohol moiety of the QAEs in AC-11® also contributes to the biological activity of AC-11®, the alcohol moiety would yield additional biologic activity to that shown for quinic acid alone. Evidence supporting this interpretation is that when AC-11 or quinic acid analogs are base hydrolyzed with 2M NaOH, about 50% of growth inhibiton of cancer cells is lost, while base hydrolysis treatment of quinic acid or quinic acid lactone had no impact on in vitro cancer cell toxicity (Table 3 in Sheng et al 2005). These recorded data (Sheng et al 2005) are consistent with the fact that the QAE's in AC-11 are related to chlorogenic acid. Clearly both quinic acid and/or its alcohol moiety esterified to it; i.e. such as the phenolic, caffeic acid, are both naturally occurring in water extracts of Uncaria (i.e. 5-caffeoylquinic acid or chlorogenic acid), and are both hypothesized to be additional actives as DNA repair enhancers. AC-11® is a neutraceutical DNA repair enhancer because it contains at least two quite different sub classes under the CAE standardization : i.e. one having QAEs (e.g. such as chlorogenic acid) and the other a still yet unidentified DNA repair enhancer relating to the alcohol moiety of QAEs.

4. MODE OF ACTION OF WATER EXTRACTS OF UNCARIA TOMENTOSA SUCH AS AC-11®

There are two products currently being sold in the marketplace based on the reference standard of quinic acid esters or quinic acid itself. They are AC-11®/C-Med-100® (CAEs and QAEs), and QuinMax™, the ammonium chelate of quinic acid (US patents 6,039,949; 6,238,675B1; 6,361,805 B2, 7,579,023; 7,595064; PCT/US2006/009394; PCT/US2007 /073261). AC-11® is commonly dosed at 350 mg per day (range = 250-700) (Lamm et al 2001, Mammone et al 2006, Pero et al 2002, 2005, Sheng et al 2000A, 2001), and quinic acid ammonium chelate (Quinmax™) at 1000 mg per day (range = 500-3000) (Pero et al 2009, Pero and Lund 2009). Given that AC-11® has been quantified to contain 8-10% CAEs (Sheng et al 2005), and assuming half the molecular weight of the QAEs is quinic acid (e.g chorogenic acid), then the daily dose of quinic acid in AC-11® would be about 25-70 mg/day (i.e. 10% of AC-11® of daily doses of 250-700 mg/day divided by 2 = 12.5 to 35 mg /day), or considerably lower than 1000 mg/day recommended for Aqua Bimini (100% quinic acid

ammonium chelate). Yet both products are well known to enhance DNA repair, anti-inflammation, and immunity as documented in his report. The logical explanation is that there are apparently other water soluble components found in AC-11® water extracts, that can either synergize the effects of quinic acid; e.g., the alcohol moiety portion of the QAEs such as the phenolic acid, caffeic acid, or yet an unidentified new bioactive that is additive or synergistic to the effects of quinic acid (postulated in this study). In other words, there are two different products. One, AC-11® that acts as a neutraceutical (chemically defined in part), and two, QuinMax™ that acts as a pharmaceutical (chemically defined), and yet both are based in large part on the efficacy of quinic acid.

a) DNA Repair Enhancement and Aging

AC-11® is essentially free of oxindole alkaloids have been shown to possess a broad spectrum of biological activity, both orally and topically, including DNA repair enhancement and anti-inflammatory benefits. These two biological mechanisms are key molecular targets to develop treatments that protect skin cells exposed to ultraviolet light from the sun (non-oxidative stress). For the reason that AC-11® is the only documented natural source of components which simultaneously up regulate DNA repair and stimulate a positive response to inflammation, studies were undertaken to show additional benefit to the skin from AC-11® treatment. The data clearly demonstrated that skin cultures co-incubation with AC-11® reduced skin cell death from UV exposure, and this protection was accounted for by a concomitant increase in DNA repair. (Mammone et al 2006, Sheng et al 2000A, Confidential Report #3). AC-11® has also demonstrated enhanced DNA repair in vivo, in vitro and in human studies after exposure to DNA- damaging chemicals (e.g. doxorubicin, hydrogen peroxide, ozone, environmental exposures). Presumably this phenomenon occurs by preventing or removing DNA damage that in turn blocks damaged cell replication (Cisneros et al 2005, Pero et al 2002, 2005, 2009A, 2009B Sheng et al 2000B, 2001, 2005). Moreover, rat white blood cells (WBC) or mouse spleen WBC were increased in vivo after AC-11® and quinic acid chelate (QuinMax) oral administration either by gavage or in drinking water from 7.1 to > 8.1 x 10^6 cells/ml, or a 13-25% increase over untreated controls in the protection of DNA from becoming damaged and killing the cells (Sheng et al 2005, Akesson et al 2005). It has been scientifically established that there is a causal effect between DNA damage and accelerated aging. If the above data were extrapolated into a human lifespan, then living to an average age of 90 years would be increased to approximately 112 years by ingesting optimal amounts of AC-11® or quinic acid equivalents during one's lifetime.

The DNA repair studies cited above are based on comprehensive analysis of the type of DNA damage that is environmentally induced and the measurable benefits. It is not just a general enhancement for the excision DNA repair enzymatic process. Rather, the enzymes being used to repair DNA depend on the type of DNA lesions being inflicted, so quantifying DNA repair relevant to one type of DNA lesion does not necessarily indicate a general DNA repair enhancement of importance to a broader anti-aging effect. We reported in a number of studies a broad spectrum of DNA repair enhancement endpoints such as: (i) single strand breaks measured by alkaline elution, (ii) thymine T-T dimers, (iii) 8-OH guanine adducts, (iv) DNA replication synthesis/cell survival measured by thymidine incorporation into DNA or cell counting or number of UV induced sun burn cells, (v) recovery from ozone injury and

(vi) serum protein thiols a surrogate estimate of the DNA repair enzyme poly ADP ribose polymerase (PARP) (Pero et al 1995) and lifespan (Pero et al 2000).

(B) Immune Function Enhancement

It has been observed that both AC-11® and a Quinic Acid Chelate (QuinMax™) enhance immune cell function by increasing the number of fully functional lymphocytes without suppressing antigenic responses to growth stimuli or inducing cell lymphocyte death by apoptosis (Lamm et al 2001, Sheng et al 2000A, Åkesson et al 2003A, 2003B, 2005). In addition, the immune modulating transcription factor, NF-kB, was inhibited by both AC-11® and a quinic acid chelate (QuinMax™). (Sandoval et al 2002, Akesson et al 2003B, 2005).

(C) Inhibition of Inflammation

As already pointed out earlier Uncaria extracts rich in alkaloids have consistently been reported for their effectiveness as anti-inflammatory treatments (Jones 1995, Reinhard 1999). There are now more than 50 dietary supplements standardized for the alkaloid content available commercially (Keplinger et al 1999) as anti-inflammatory agents. However, none of these products were prepared as hot water extracts such as AC-11®, which follows the historical folk medicine practices. Whereas we have reported that alkaloid-containing Uncaria sp. products have greater toxicity than AC-11® (Sheng et al 2000A), we have also determined that both AC-11® and quinic acid chelates are potent inhibitors of NF-kB and thus potent anti- inflammatory agents, along with reduced toxicity (Akesson et al 2003B, 2005). This work has been confirmed by in vivo reports (Sandoval-Chacon et al 1998, Sandoval et al 2000) conducted on water extracts of Uncaria sp. not standardized to CAEs (Miller et al 2005, Piscoya et al 2001). These non-standardized water extracts also had greatly reduced alkaloid content providing further evidence that compounds other than alkaloids are primarily responsible for the anti-inflammatory activity observed.

(D) Anti-Oxidation

Endogenous generated oxidative stress in the form of hypochlorous acid strongly inhibits DNA repair when estimated by a variety of procedures for quantifying DNA repair; e.g unscheduled DNA synthesis (UDS), inhibition of poly ADP ribose polymerase (PARP, repair of strand breaks assayed by nucleoid sedimentation or alkaline elution (Pero et al 1996). Moreover, oxidative stress evaluated by the level of thiols in serum correlates strongly to most human diseases including cancer, cardiovascular disease, diabetes, and inflammation (Banne et al 2003) and prognosis of HIV infection (Marmor et al 1997). Both AC-11® (Pero et al 2002, 2005) and Quinmax™ (Pero et al 2009) clinical treatments have demonstrated the ability to prevent oxidation via an increase in serum protein thiol analyses that estimates levels of in vivo oxidative stress. Ozone, an oxidative stress environmental toxin, causes cellular damage which in turn is reduced in mice by an aqueous extract of Uncaria tomentosa (Cisneros et al 2005).

(E) Neurogenic Effects

Alzheimers, mood, and psychological stress (lifestyle factors) have been shown to be mediated by water extracts of Uncaria sp. Examples include amyloid body inhibition (Castello 1998, 2005, 2006) and increased serum tryptophan levels, the serotonin precursor (Pero et al 2009). These psychotropic observed benefits were also independent of their indole alkaloid content.

4. AVAILABLE PUBLISHED DATA IN THE SCIENTIFIC LITERATURE FOR UNCARIA SP

Water soluble extracts and/or water soluble components of Uncaria sp. have been shown to be responsible for medicinal benefits. There are 3 main sources of data available for evaluation of this efficacy. They are in vitro, rodent and human studies. Taken together the evidence is strong that aqueous components in Uncaria tomentosa, specifically AC-11®, provide effective clinical treatments for many ailments and disorders in humans.

First, there are peer reviewed in vitro data that HL-60 leukemic, K-563 leukemic, Jurkat, and Raji cells, MCF 7 beast cancer cells, murine macrophage RAW 264.7 cells, allium cells, Chinese hamster ovarian cells, and rat ascites hepatoma cells were all shown to be positively affected by Uncaria sp. water extracts (Kuras et 2009, Riva et al 2001, Sandoval et al 2002, Santa et al 1997, Sheng et al 1998, Yagasaki et al 2000, Akesson et al 200B).

Second, DNA repair, immune enhancement enhancement, anit-inflammation, recovery from doxorubicin chemotherapy, and improvement in overcoming Listeria monocytrogenes infection were all successfully treated in rodents with water extracts of Uncaria sp.. (Aguilar et al 2002, Cisneros et al 2005, Eberlin et al 2005, Sheng et al 2000A, 2000B, 2005, Akesson et al 2003A, 2003B, 2005)

Third, over 200 human volunteers in total were administered a daily dose of AC-11® or another water extract of Uncaria species between 250 to 7000 mg/day that stimulated immune response, DNA repair and/or anti-inflammation without presenting with any side effects (Lamm et al 2001, Miller et al 2005, Piscoya et al 2001, Pero et al 2002, 2005, 2009, Sheng et al 2000A, 2001). It appears obvious that Uncaria sp. water extracts are safe and efficacious for further clinical evaluation.

Rodent total dose treatment ranges that have been tested for AC-11® and other water extracts of Uncaria ranged from 400 to12,000 mg/kg (Aguilar et al 2002, Cisneros et al 2005, Eberlin et al 2005, Sheng et al 2000A, 2000B, 2005, Akesson et al 2003A, 2003B, 2005). Although weight loss has occurred at the total dose of AC-11® of 5,600 mg/kg in humans (Pero et al 2005), rodent studies did not confirm weight loss by any mechanism (Pero et al 2005), thus indicating a positive benefit from AC-11® treatment. In fact no significant toxicity was observed in rodents even when evaluated by a complete histopathological examinaton (Sheng et al 2000A).

Furthermore, there were efficacious indications at all doses tested of Uncaria water extracts in rodents which were total doses ranging from 720-12,000 mg/kg (Aguilar et al 2002, Cisneros et al 2005, Eberlin et al 2005, Sheng et al 2000A, 2000B, 2005, Akesson et al 2003A) . Compared to the dose range for human efficacy studies which was total doses

ranging from 80-601 mg/kg (Lamm et al 2001, Pero et al 2002, 2005, Sheng et al 2000A, 2001), the rodent model values were generally higher than was needed in humans presumably because of body surface area differences. It is well known that the greater the surface area of a mammal available for adsorption, the greater will be the efficiency of adsorption. The body volume in humans is much higher than in rodents, thus providing a higher absorptive potential being roughly 70 kg versus 0.250 kg, respectively. Therefore, it was concluded that the rodent studies generally supported the data obtained in humans for both toxicity and efficacy.

The human clinical studies performed so far after supplementation with either AC-11®, Quinmax™ or other water extracts of Uncaria sp., have demonstrated a broad range of efficacious responses such as: (i) increased serum protein thiols (antioxidant protection), (ii) increased urinary nicotinamide and tryptophane levels, (iii) increased number of WBC, (iv) increased pneumococal titer, (v) DNA repair enhancement, (vi) increased lymphocyte growth response, (vii) reduced level of 8-OH quanine DNA adducts, (viii) weight loss, (ix) reduced sunburn, (x) increased removal of UV-induced thymine T-T dimer DNA damage, (xi) improvement in life style-induced clinical responses and (x) osteoarthritis relief in the knee (Lamm et al 2001, Mammone et al 2006, Miller et al 2005, Piscoya et al 2001, Pero et al 2002, 2005, 2009, Pero and Lund 2009, Sheng et al 2000A, 2001). The data presented supports at least 4 different modes of action; namely DNA repair, immune enhancement, inhibition of inflammation and anti-oxidation after treatment with either AC-11® or QuinMax®. The broad spectrum of clinical responses documented by these peer-reviewed articles supports the health benefits associated with thee commercially available preparations.

5. CONTRAINDICATIONS

There are over 30 reports dealing with the efficacy and toxicity of water soluble Uncaria sp. products which includes cells, tissues, rodents and humans. In all these studies there were no toxic side effects observed from the hundreds of observations in animals and humans. Apart from occasional weight loss documentation there have been no other symptoms recorded. On the other hand, indole alkaloid extracts often have been associated with toxic side effects (Aquilar et al 2002; Pilarski et al 2005).

6. DISCUSSION

The scientific evidence behind water soluble Uncaria sp. extracts has now been presented independent from their oxindole alkaloid content. This was accomplished by standardizing water soluble AC-11® to the bioactive ingredients identified as CAEs (8-10 %) that was in turn depleted of containing any significant amounts of the bioactive oxindole alkaloids. (< 0.05%) As the water soluble Uncaria extract AC-11® became more clearly delineated chemical, first identified as CAEs (8-10%), then as QAEs (4-5 %) and then to QA (2-2.5 %) by assuming ½ the MW of QAEs was QA (Sheng et all 2005). Because “folk” medicine practice used water extracts comparable to AC-11®, and they have insignificant alkaloid

content, there seems little doubt that QA and QAE-based Uncaria sp. extracts (e.g. AC-11®) are predominantly responsible for the observed Uncaria sp. efficacy over the years.

Although widely distributed in nature and plant foods, quinic acid has not previously been recognized to have any nutritional benefits until it was discovered to be a bioactive ingredient of C-MED-100®/AC-11®. This is an important point when considering quinic acid safety and efficacy. Although not previously recognized as a significant component to our food chain, Quinic Acid has nonetheless been present as a major health component in many foods affecting the basic nutritional health status and metabolism in man. (Pero et al 2009).

QA is a well-known key metabolic intermediate in the synthesis of plant aromatic compounds including aromatic amino acids that is essential to animal life. It is called the shikimate pathway (Hermann et al), and relates directly to human metabolism because the GI tract microflora produces QA everyday or utilizes the QA content from food. Interestingly quinic acid equivalents are mainly found in brightly colored foods (i.e. reds, oranges, greens, yellows) vegetables and fruits which are well known to be exceptionally healthy food sources; for example, such as prune, kiwi, sea buckthorn, coffee, cranberry, lingonberry, blueberry, wortleberry, red/yellow tamarillo, sultana, quince, sunflower, nectarine, peach, pear, plum, honey, black currant, medlar, apricot, asparagus, mushroom and green olive (Van Gorsel et al 1992, Beveridge et al 1999, Englehardt et al 1985, Graham et al 1992, Jensen et al 2002, Romero Rodrigues et al 1992, Lewis et al 1995, Silva et al 2002, Mourgue et al 1975).

The recent discovery that QAE's™/Quinmax™ can increase the synthesis of tryptophan and nicotinamide is a major development to the area of clinical nutrition. In fact, certain foods or AC-11® and QA chelates (QuinMax™) when administered to humans as a dietary supplement may be an effective way effective to enhance essential aromatic amino acid biosynthesis, via endogenous biosynthesis by gastrointestinal (GI) microflora (Hermann and Weaver 1993, Hermann 1995, Pero et al 2009). Such a novel approach to clinical nutrition has never before been postulated or otherwise known. This concept would revolutionize how we treat most illnesses since their origins would have in common basic metabolic mechanisms that regulate energy, plus hormone and protein synthetic events. The data presented provides strong evidence that AC-11® contributes to human nutritional enhancement as a dietary supplement based upon its high content of QA and QAEs™. Due to the potential importance to human health, and since AC-11® has these basic nutritional compositional properties, studies are underway to confirm this nutritional utility of AC-11®. As a dietary supplement AC-11® supplies QA and QAE's™ to the diet. It would be more economical and practical, than supplying pure QA, which to date has not been synthesized on a commercial scale.

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