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IASC 30 years

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In This Issue

DIRECTOR'S MESSAGE

Message from Interim Executive Director Jane Wilson


Jane Wilson, Interim Director

Hello IASC members! I want to thank all of you for your support and well wishes as I have transitioned into the role of the IASC interim executive director. Summer seems to be going by so quickly (I say this every year), and soon we'll be enjoying cooler temperatures and sending kids back to school. I have a son in college (sophomore) and a daughter in high school (junior), and we'll be making those transitions at my house in the next few weeks.

I'll start by mentioning the March 2014 IASC Board of Directors meeting held at Expo West in Anaheim, CA. Jasen Lavoie of Pharmachem Labs was welcomed to the board as a new director. I also want to acknowledge Bill Pine of Improve USA and his years of service to IASC and the Board of Directors as he finished his term. The March board meeting also continued strategic planning discussions that were initiated in late 2013.

Working group meetings in May and June of this year have helped move the strategic planning process forward at a quick pace. With the challenges of the NTP study results having been managed, there is a renewed sense of the need to fully engage the IASC membership, and focus on activities that benefit the industry as a whole. I will spend the next few months refining several of the ideas that were proposed for presentation at the next board meeting in October. Thanks again to Don Lovelace and the staff at Lily of the Desert Nutraceuticals who hosted the June working group meeting at the Lewisville, TX facility.

A primary focus of the strategic planning process is a recommitment to the generation of aloe vera science that supports current uses and encourages the expansion of products manufactured using this botanical. As was recently announced to the membership, the Science & Technical Committee is being re-established to undertake the task of charting a course of aloe vera scientific research to be considered by the board over the next few years. If you or a scientific colleague in your organization has an interest in contributing to the future scientific initiatives of the council, please contact me at your convenience.

The strategic planning process has also included discussion about IASC communications. As one part of that topic, I'll be seeking to diversify the types of information disseminated in this newsletter. I'd love to hear from you if you have an idea for an article that may be of interest to the IASC membership (especially if you are willing to write it!). This is your newsletter, and I want the content to reflect the topics of most interest to the IASC membership, including international issues that impact the aloe vera industry.

I hope to meet many of you at the SupplySide West trade show in Las Vegas, where the IASC board will meet on Friday, October 10. This year the trade show will be held at the Mandalay Bay facility. If you'll be at the show and would like to connect, please feel free to contact me via email or at 734-476-9690.

SPECIAL TOPICS

'FDA Inspections & Emerging cGMP Compliance Issues' teleseminar now available

The American Herbal Products Association's (AHPA) two-hour teleseminar "FDA Inspections & Emerging cGMP Compliance Issues for Dietary Supplements," held on May 15, is now available for purchase at the AHPA online bookstore. Materials for sale include the audio recording and PowerPoint presentation.

The two-hour teleseminar includes tips for handling every aspect of a Food and Drug Administration (FDA) inspection—from pre-inspection preparation to interacting with on-site inspectors—and how to respond to observations and warning letters. This is part of AHPA's cGMP Compliance Series, designed to help the dietary supplement industry understand and efficiently comply with current good manufacturing practices (cGMPs) and regulations (21 CFR 111).

This teleseminar includes insiders' views of the cGMP enforcement landscape from veteran industry legal experts, while AHPA staff offer a detailed analysis of data from recent inspections.

AHPA's general counsel, Tony Young, Esq., of Kleinfeld, Kaplan & Becker, offers several tips for companies being inspected by FDA.

AHPA's chief information analyst, Merle Zimmermann, Ph.D., provides an analysis of 506 FDA inspections performed from 2008 to 2013. Dr. Zimmermann's analysis reveals that the exact same issue identified by inspectors could result in either a Form 483 or a discussion item in an Establishment Inspection Report (EIR). In some of the reviewed cases, when a company took action to address the issue while the inspection was in progress, FDA inspectors recorded the issue as an EIR discussion item rather than a Form 483.

Justin Prochnow, Esq., of Greenberg Traurig, gives an overview of recent FDA warning letters to supplement companies, offering insight into FDA's enforcement priorities. Prochnow reminds listeners that FDA warning letters are not proof of violations; they are only FDA's opinion. He also reviews the top 10 alleged cGMP violations according to recent warning letters.

Marc Ullman, Esq., partner at Ullman, Shapiro & Ullman, provides tips for preparing for an FDA inspection. He recommends companies educate employees about FDA inspections and establish standard operating procedures for an inspection. He also stresses that companies should document everything because, "if it's not in writing, it didn't happen."

Ashish R. Talati, Esq., member of Amin Talati LLC, shares tips for drafting an effective written response to an FDA Form 483. He notes that a written response is not required—but it is in a company's best interest to respond. He also reviews common pitfalls for companies to avoid.

For more information about this teleseminar and others in AHPA's cGMP Compliance Series, visit the AHPA online bookstore or contact Haley Chitty at 301.588.1171 x104.

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Originally published in the August 2014 AHPA Report.

AHPA NDI Database shows 10 of 40 recent NDI notifications acknowledged by FDA without objection

The American Herbal Products Association (AHPA) recently received partial information on 40 new dietary ingredient (NDI) notifications submitted to the Food and Drug Administration (FDA) between November 2012 and February 2014. Ten of these notifications were acknowledged by FDA without objection.

AHPA's

Botanical Safety Handbook

Second Edition

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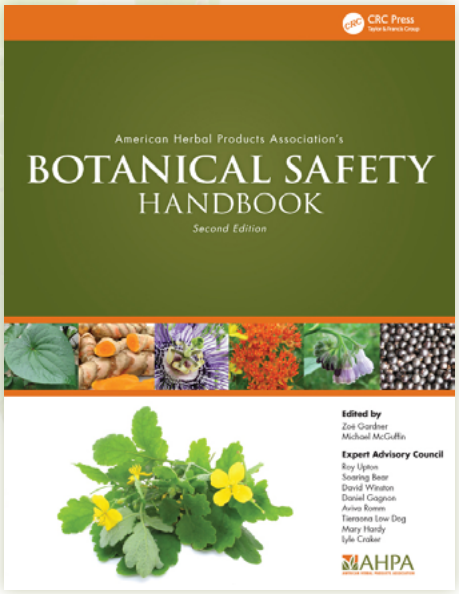

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The recently received data have been analyzed and entered into AHPA's NDI Database, which now contains 710 NDI notifications and summaries of FDA's responses when available. The database enables users to search notifications by company and ingredient, including common or Latin names for botanicals. An "Outcome Statement" is also provided to help users quickly understand FDA responses, including any issues that resulted in FDA objections.

Companies that want to use a dietary ingredient not marketed in the U.S. before Oct. 15, 1994 are required to submit an NDI notification explaining why the ingredient is reasonably expected to be safe. This notification must be submitted at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce.

FDA does not "approve" or "disapprove" NDI notifications. Instead, the agency generally provides one of several types of responses. According to FDA, examples of these responses include, but are not limited to: (1) letter of acknowledgement without objection; (2) letter listing deficiencies that make the notification incomplete; (3) objection letter raising safety concerns based on information in the notification or identifying gaps in the history of use or other evidence of safety; and (4) letter raising other regulatory issues with the NDI or dietary supplement (e.g., the NDI is not a dietary ingredient as defined by regulation or the product is excluded from the definition of "dietary supplement" under current regulations because it is not intended for ingestion.

"The fact that one in four NDI notifications were acknowledged by FDA without objection demonstrates that companies are effectively navigating the NDI system in order to meet consumer demand for innovative and safe dietary supplement ingredients," said AHPA Chief Information Analyst Merle Zimmermann, Ph.D., who manages the NDI Database. "AHPA's NDI Database helps companies effectively navigate the NDI notification process and avoid common pitfalls that can result in FDA objections."

Additional information about the NDI Database and other NDI-related resources is available online.

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Originally published in the July 2014 AHPA Report.

AHPA launches free Botanical Identity References Compendium

The American Herbal Products Association (AHPA) has launched the AHPA Botanical Identity References Compendium as a resource for manufacturers and researchers to accurately identify botanical ingredients.

The AHPA Compendium is a cooperative and centralized source of information on physical characteristics and test methods that can be used by qualified and experienced analysts to determine the identity of plant species and articles of trade obtained from these plants. It currently provides such information for nearly 200 commonly used botanical species and will continue to be expanded by AHPA staff and participating contributors.

The AHPA Compendium provides examples of unique identifying characteristics and specific analytical methods for each of the listed species that may be applicable to the plant itself or to natural products produced from the plant. This information is presented in one or more of the following fields:

- Voucher specimen images
- Organoleptic descriptions
- Macroscopic images and descriptions
- Microscopic images and descriptions
- Chromatographic methods (e.g., TLC, HPTLC, HPLC)
- Reviews of certain known adulterants
- Links to abstracts of relevant publications

This free, publicly accessible resource combines materials from open-source academic documents with information generously donated by Alkemist Labs, American Herbal Pharmacopeia, Botanical Liaisons, CAMAG Laboratories, ChromaDex, GRACE, the HPTLC Association, Mountain Rose Herbs, PlantaPhile, PhytoLab, and U.S. Pharmacopeia.

AHPA encourages labs, companies, educational institutions, and other organizations to contribute additional information to increase the scope and depth of this resource. The AHPA Compendium was built on an expandable platform that will incorporate additional methods and botanicals developed and donated by industry experts. An advisory panel will use a rigorous vetting process to evaluate all information that is posted to the Compendium.

"The AHPA Compendium is an evolving tool that will respond to the changing needs of its users to provide timely and relevant information," said Merle Zimmermann, PhD, AHPA's chief information analyst, who oversees the Compendium. "As more information is contributed and the website grows, it will be an increasingly valuable tool to verify

the identity of herbal ingredients."

"Botanical authentication has always been a top priority for AHPA and the herbal products industry," said Maged Sharaf, PhD, AHPA's chief science officer. "Providing the means to accurately and efficiently identify ingredients is just one of the ways AHPA serves its members and the industry at large."

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Originally published in the June 2014 AHPA Report.
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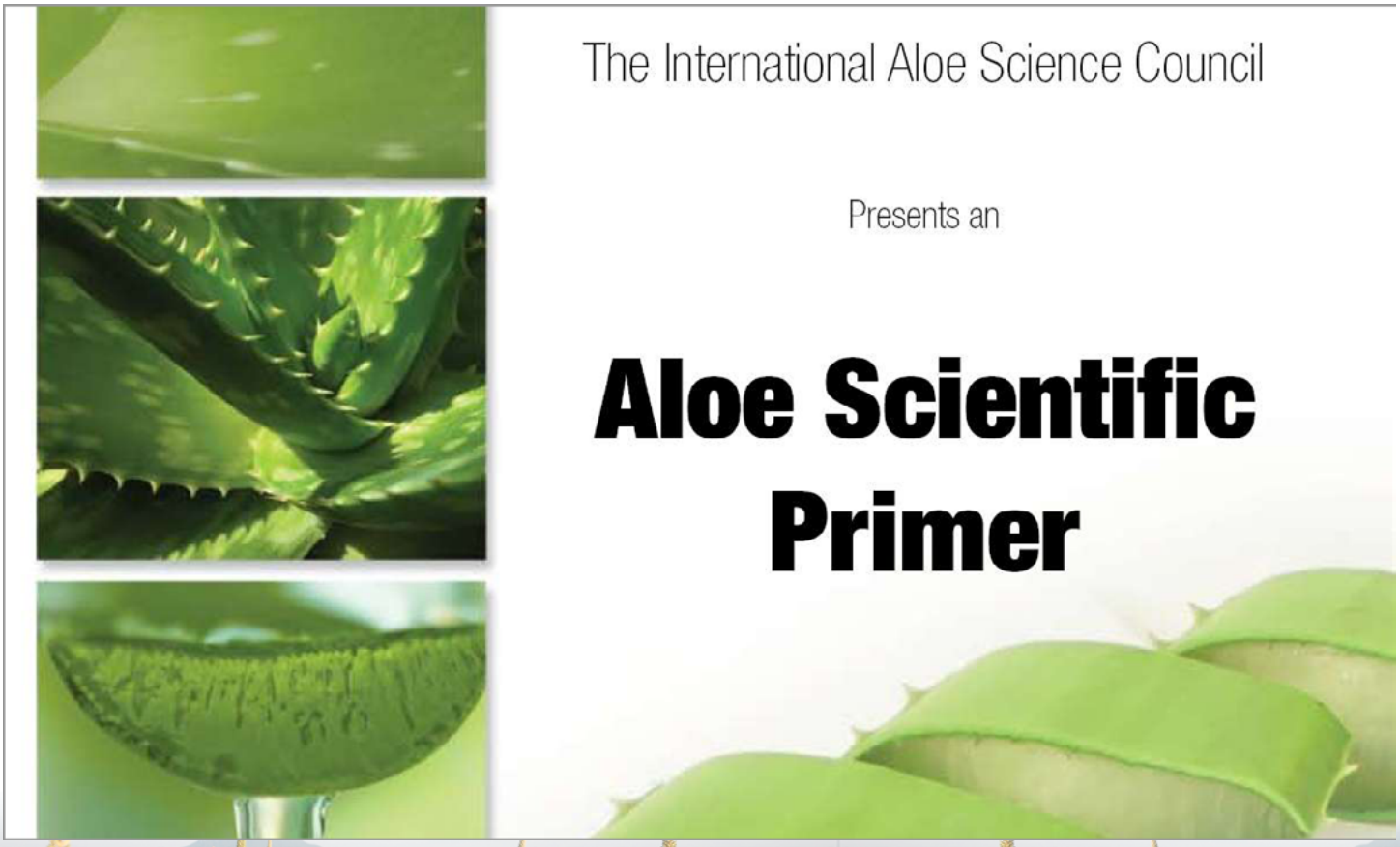
AHPA International Committee, IADSA staff discuss regulatory issues

AHPA's International Committee conducted a teleconference to provide an update on the latest supplement regulatory developments around the world and to acquaint its members with the work of the International Alliance of Dietary/Food Supplement Associations (IADSA).

AHPA is a long-time and active member of IADSA, an alliance of more than 50 food supplement associations from six continents that works closely with governments and international organizations to ensure that the food supplement industry is represented in the development of international supplement policies.

"To promote the responsible commerce of herbal products internationally, it is critical for the dietary supplement industry to participate in global regulatory discussions," said Steve Holmes, chair of AHPA's International Committee and regulatory affairs manager at Metagenics. "The wide range of regulations presents challenges to supplement importers and exporters. Complete global harmonization of regulations is a lofty goal, but IADSA and AHPA are working diligently on issues such as stability guidelines, product quality, health claims, and, of course, botanicals and their constituents. There are great international opportunities, so I encourage all AHPA members to join this effort."

Cynthia Rousselot, IADSA's director of technical and scientific affairs, provided a summary of the regulatory landscape in the European Union, noting that there is a lack of clarity for botanicals. Traditional use claims are allowed, but claims for botanicals not considered Traditional Herbal Medicine have not been defined. The European Food Safety Authority is working on guidance to help clarify rules for botanicals. Discussions surrounding health claims are still ongoing and



quite contentious. Setting the maximum levels for vitamins and minerals is highly controversial and is still being negotiated. There probably won't be any resolution until after the EU parliamentary elections.

Michelle Stout, Amway/Nutralite's regulatory policy director, provided an overview of regulatory issues in China and Japan. Stout said the Japanese prime minister is looking to improve food claims specifically regarding health and expand functional claims so consumers can see their value. An expert panel is investigating a system for structure/function claims similar to that of the U.S., but there is opposition from some who believe that the current FOSHU approach should be used, with manufacturers being responsible for providing safety. This discussion will be continued at next month's meeting to determine whether the FOSHU approach should be continued or the report's recommendation to move to a U.S.-based approach should be accepted.

The health food category in China covers supplements and functional foods. The registration process is very lengthy, but there are revisions in the food safety law to improve the notification and registration process. Further discussions are needed to determine which foods fall under notification, how to substantiate, and what is considered appropriate science.

Ric Hobby, IADSA chairman and Herbalife's vice president of worldwide regulatory, government and industry affairs, gave an overview of the regulatory environment in Southeast Asia. There are 10 nations in the Association of Southeast Asian Nations (ASEAN) working to harmonize standards in 11 areas, including traditional medicine and supplements. The Scientific Committee, Framework Task Force, and GMP Task force of the ASEAN Consultative Committee for Standards and Quality Traditional Medicines and Health Supplements Product Working Group met in March. Although the committee did not complete pending technical requirements such as safety data requirements and limits of microbial contaminants, significant progress was made.

David Piñeda, IADSA's director of regulatory affairs, explained that most Latin American countries have unique regulations, which will make harmonization a challenge, especially for botanicals. However, a recent trade accord that removes tariffs on 92 percent of trade has been signed by the Pacific Alliance, the regional trade block comprised of Chile, Colombia, Mexico, and Peru. This agreement will have a direct impact on supplements, as the Pacific Alliance established the need to develop Guidelines for the Approximation of Regulations on a number of priority sectors. Pacific Alliance member governments have requested their National Industries Chambers to develop and provide a proposal for Guidelines for the Approximation of Food Supplements Regulations.

IADSA also provided an update on its Technical Group and Scientific Council. The Technical Group has focused on quality and contamination issues and global guidance for adverse event reporting, among other issues. The Scientific Council has worked on a number of issues, including health claims and maximum safe levels of active ingredients in products.

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IASC AND ALOE IN THE NEWS

- Aloe Vera: The Next Superstar of the Plant World, Natural Products INSIDER
- Natural remedies for common pregnancy ailments, FoxNews.com
- The 10 Best Beauty Products To Buy At Trader Joe's, Huffington Post
- Herbal drink believed to prevent and treat cancer, National News Bureau of Thailand
- Home Remedies to Fight Skin Pigmentation, IDIVA.com
- Elixir of health, The Hindu
- Inexpensive home remedies for fighting dry skin and eczema, MyFoxHouston.com
- Mocktails Come of Age, The Wall Street Journal
- 'Waterwise' project takes root in Rollingwood, Statesman.com
- Call to conserve medicinal plants, The Hindu
- Razor Burn Is The Worst, So Here's How To Prevent It, Huffington Post
- Tomm McKinney: Be careful when selecting herbal supplements, Lebanon Democrat
- Post-cancer spa days: healthy eating, skin care and plant oestrogens, The Telegraph
- Living Out Loud, Tri County Leader
- Halton man learns about frostbite dangers the hard way, insideHalton.com
- Cover up: Frostbite can do more than nip at fingers, toes and nose, doctors say, Montrealgazette.com
- Why I Decided To Ditch Chemicals And Go Organic With My Hair Dye, Huffington Post

LEGAL & LEGISLATIVE NEWS

Congressional Outlook

By Pete Evich, AHPA National Legislative Consultant, Van Scoyoc Associates

Congress is on recess this week for the 4th of July holiday, and only 28 scheduled session days remain in the time between their return and the midterm elections. Congress will take the entire month of Aug. off, half of September, and all but two days of Oct. A multi-week, post-election lame duck session will convene sometime shortly after the November elections and end before Christmas.

The Congressional clock has run out on any significant legislation (immigration reform, tax reform, housing finance reform, etc.). The priority issues between now and the elections are addressing a looming highway funding crisis, enacting annual federal spending bills due on October 1, and the debate over how the U.S. should address developments in Iraq. Congress is also under pressure to hash out legislation that would reduce veteran wait times for health care and stop a rash of preventable deaths among veterans.

The federal highway fund is expected to go broke at the end of Sept., which threatens to disrupt hundreds of highway construction projects across the U.S. Lawmakers will have to find at least $12 billion to keep the fund solvent for another 9 to 12 months.

Election year politics are mudding the chances of Congress to make significant progress on its annual spending bills. The breakdown, which is happening in the Senate, is over amendments that vulnerable Democratic members would rather avoid having to take votes on before the Nov. elections. This stalemate comes despite a budget agreement hammered out late last year that covered 2014 and 2015 fiscal spending bills. While the Senate voted to agree on those top-line spending figures, moving appropriations on the floor has proven to be too much for lawmakers.

The budget breakdown makes it inevitable that Congress pass a continuing resolution to keep at least some areas of government funding at current levels into the new fiscal year, which begins Oct. 1.

Lawmakers will spend a significant amount of time continuing to monitor and debate how President Obama should handle the situation in Iraq as well as the transition in Afghanistan which no policymaker wants to see become another Iraq.

House Republican leadership shakeup

The biggest news in Washington this summer was the unexpected and shocking 11 point primary defeat of House Republican Majority Leader Eric Cantor (R-VA) by economics professor, Dave Brat, on June 10.

The day after his defeat, Rep. Cantor resigned his position as House Majority Leader, effective July 31. House Republicans scheduled leadership elections for June 19. Since House Majority Whip Kevin McCarthy (R-CA) immediately through his hat in the ring for the Majority Leader post, the elections were for both the Majority Leader and Majority Whip positions.

House Republicans promoted McCarthy to House Majority Leader and elected Rep. Steve Scalise (R-LA) to replace McCarthy as Whip. There will be another round of elections for the entire slate, including Speaker, in Nov. after the midterm elections. While there is almost no chance that Democrats will win the House in the midterms (Republicans currently have a 17-seat majority), it is very possible that if the House Republicans lose some seats, the entire House Republican leadership could see a challenge in Nov. At this point in time, House Republicans are predicted to pick up a handful of seats in the midterms.

What will be interesting to see is if, in the wake of Cantor's defeat, the House GOP will view this as more of a one-off or as a result of Cantor not being sufficiently conservative on immigration reform, Obamacare, the debt ceiling, and other issues. Either way, House GOP incumbents will be sure to pay much closer attention to Tea Party activists in their districts.

DASCA sees action in the House

Legislation to crack down on anabolic steroid products is starting to see Congressional action. The Designer Anabolic Steroid Control Act (DASCA), which is supported by the American Herbal Products Association (AHPA) and the other major industry trade associations, was first introduced in this Congress by Sens. Sheldon Whitehouse (D-RI) and Orrin Hatch in Feb. of this year. Three months later, DASCA was introduced on the House side by high ranking Energy and Commerce Committee members, Reps. Joe Pitts (R-PA) and Frank Pallone (D-NJ). Reps. Pitts and Pallone are the chairman and ranking member (respectively) of the Energy and Commerce Committee's Health Subcommittee. Pitts and Pallone's leadership positions on the panel helped to gain quick action on the measure. On June 19, just a few weeks after the bill's introduction in the House, the legislation passed out of the House Energy and Commerce Subcommittee on Health. A full Energy and Commerce Committee markup of the bill is likely to occur in July.

DASCA is strongly supported by all the major dietary supplement trade associations because it would close a loophole exploited by steroid manufacturers to sell products that claim to be all-natural muscle builders when they may actually contain chemically altered versions of anabolic steroids. DASCA would provide the Drug Enforcement Administration with new authority to place designer anabolic steroids on the Controlled Substance Schedules more rapidly, as well as providing that agency with new enforcement tools to prosecute disreputable companies that develop and market anabolic steroids as products labeled as dietary supplements.

Hopefully, the positive momentum that DASCA is experiencing in the House will increase the bill's prospects for passage on the Senate side. AHPA helped to bring the DASCA bill to the attention of Sen. Martin Heinrich (D-NM), who ultimately decided to cosponsor the Senate version of the measure on May 7.

The Senate's DASCA bill number is S. 2012 while the House bill is H.R. 4771. AHPA will continue to keep its membership informed as significant developments occur on this legislation.

Sen. McCaskill takes Dr. Oz to the woodshed

On June 17, the U.S. Senate Committee on Commerce, Science and Transportation's Subcommittee on Consumer Protection, Product Safety, and Insurance held a hearing titled, *"Protecting Consumers from False and Deceptive Advertising of Weight-Loss Products."* The hearing was led by the Chair of the Consumer Protection Subcommittee, Sen. Claire McCaskill (D-MO).

McCaskill was one of 20 Sens. to vote for the 2012 Durbin amendment that would have imposed product registration on dietary supplement manufacturers. While in the Nov. column, we had been unclear about her interest in this topic, we knew that she has been critical of this category of supplements. Others participants included Sens. Dean Heller (R-NV), Amy Klobuchar (D-MN) and Richard Blumenthal (D-CT).

From the onset it was clear that the hearing served as a forum for Chairman McCaskill to lambast Dr. Mehmet Oz, the popular host of "The Dr. Oz Show," for comments he made a couple years ago in support of the weight loss benefits of green coffee bean extract, garcinia cambogia and raspberry ketone. McCaskill attacked Dr. Oz for calling green coffee bean extract a "miracle in a bottle" to burn fat.

Dr. Oz defended the claims made on his program and emphasized that his support for these products or ingredients was in a broader context of maintaining a healthy diet and regular exercise. He also made clear that advertisers using his statements to promote their products were doing so without his endorsement or permission.

While this interplay with Dr. Oz represented about 95 percent of the hearing's content, of potential interest to the industry were the comments of Ms. Mary Engle, Associate Director for the Federal Trade Commission's (FTC) Bureau of Consumer Protection in regard to the FTC's dietary supplement substantiation guidelines. In response to a question from Ranking Member Dean Heller, Engle reiterated the FTC's position that weight loss and other type of product claims require at least one well-controlled clinical study in support of their claims. However, the FTC may require two well-controlled clinical studies as part of a consent decree or judicial enforcement action. Here is an excerpt of Ms. Engle's response:

> "The basic law is that companies must have a reasonable basis for the advertising claims that they make at the time they make those claims. What constitutes a reasonable basis will depend on the product and the claim. In the case of products that promise health benefits, the commission has required competent and reliable scientific evidence, and then, again, what constitutes competent and reliable scientific evidence will vary depending upon the claim.

So, for example, a claim that a product will prevent cancer or treat cancer, for example, will require a higher level of evidence than a - than a claim that a product will smooth dry skin. So, in the case of weight loss products, in particularly, based on the factors we consider and consultation with experts we've determined that a randomized, control clinical studies are needed in order to substantiate a claim that a given product will cause weight loss.... But once we have determined that a company has violated the FTC Act, has made unsubstantiated weight loss claims, and they're now under order, we have put in a requirement that going forward they should have two studies. And these kinds of studies for weight loss do not need to be particularly long-term; they're not particularly expensive relative the amount of money that can be made for these products. And, given the level of fraud that we have seen in this area, it's important to have the extra assurance of a second study to ensure that, you know, this is a real result that this wasn't due to some fluke or inadvertent bias or something like that in the study.

Specifically related to the FTC's dietary supplement guidelines, Engle maintained that the agency's guidelines are written broadly "*to cover the full range of dietary supplements that may be offered, and the full range of claims that may be made for them.*" And when the agency is undertaking an investigation of a specific product, "*we know what claims were made for them, what the ingredients are, and then we have a record on which to base other requirements for substantiation for claims going forward.*"

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Supreme Court rules Coca-Cola product name challenge can proceed even if lawful under FDA regulations

By Daniel R. Dwyer Kleinfeld, Kaplan and Becker LLP and AHPA General Counsel

Today the Supreme Court issued its decision in the "POM v. Coke" case. The Court's holding will likely increase the importance of private litigation as a means of "regulating" or challenging claims for many dietary supplements, foods, OTC drugs, cosmetics and medical devices.

In this Lanham Act (unfair competition) lawsuit, POM challenged the label of Coke's Minute Maid juice that bore the name "Pomegranate Blueberry flavored blend of 5 juices." POM argued that the name and other aspects of the label were misleading because the product contained only 0.3% Pomegranate juice and 0.2% blueberry juice. Coke argued that the name complied with FDA regulations promulgated under the Federal Food, Drug, and Cosmetic Act (FDCA), and therefore a Lanham Act lawsuit was precluded.

The Court emphatically supported POM's position in a unanimous decision (Justice Breyer did not participate).

The Court held that the Lanham Act and the FDCA do not preclude each other but "complement each other." "Although both statutes touch on food and beverage labeling, the Lanham Act protects commercial interests against unfair competition, while the FDCA protects public health and safety." Thus, the two can co-exist comfortably.

In particular, the Court said that some variability in rules between the Lanham Act and the FDCA is acceptable: "Although the application of ... the Lanham Act by judges and juries in courts throughout the country may give rise to some variation in outcome, this is the means Congress chose to enforce a national policy to ensure fair competition."

Importantly, the Court also rejected the government's amicus position in the case. The government had argued that a Lanham Act lawsuit should be precluded to the extent that FDA regulations specifically authorize the challenged aspects of the label - so the Minute Maid product name could not be

challenged, but other aspects of the label could. The Court said no, FDA regulations do not alter Lanham Act rights. "An agency may not reorder federal statutory rights without congressional authorization."

It seems obvious that this decision will encourage Lanham Act lawsuits against FDA-regulated products. This could work to the benefit of a company to the extent that it may wish to challenge competitors. Of course, this does not make such lawsuits any more palatable in terms of their troublesomeness or expense.

Will this decision weaken the argument that consumer class-action lawsuits brought under state law are preempted by FDA regulations? Probably so. Although the Court is careful to note that this is not a preemption case, its analysis clearly favors a narrow reading of the FDCA's preemption provisions and clearly encourages the coexistence of different legal rules governing FDA-regulated products. The Court said, "The centralization of FDCA enforcement authority in the Federal Government does not indicate that Congress intended to foreclose private enforcement of other federal statutes" - and the same could be said of state statutes.

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In vivo monitoring of oxidative burst on aloe under salinity stress using hemoglobin and single-walled carbon nanotubes modified carbon fiber ultramicroelectrode

ABSTRACT

Single-walled carbon nanotubes (SWCNTs) and hemoglobin (Hb) modified carbon fiber ultramicroelectrode (CFUME) were employed to construct a direct electron transfer based *in vivo* H2O2 sensor. At the low working potential of -0.1 V, Hb/SWCNTs/CFUME showed a dynamic range up to 0.405 mM with a low detection limit of 4 μM (S/N=3) and a high sensitivity of 1.07 log(A) log(M)(-1) cm(-2). The apparent Michaelis-Menten constant (Km, app) was estimated to be as low as 1.35 mM. Due to the extremely small dimension and low working potential, Hb/SWCNTs/CFUME could give directly amperometric *in vivo* monitoring of H2O2 in aloe leaves with salt stress for 19.5h without the requirement of complex data processing and extra surface coatings to avoid interferences. The sharp increase of H2O2 level in aloe leaves with salt stress was clearly observed using Hb/SWCNTs/CFUME from 12.5 h, while in the aloe without salt stress, H2O2 level remained stable in the whole measurement. For further confirming the *in vivo* response of Hb/SWCNTs/CFUME, catalase (CAT) was injected into the spot adjacent to the sensor and caused rapid current decrease, which suggests the scavenging of H2O2. These results indicate that Hb/SWCNTs/CFUME can be a powerful tool for *in vivo* investigation of ROS.

Formulation development, optimization and evaluation of aloe vera gel for wound healing

ABSTRACT

PURPOSE: To formulate and optimize a herbal gel of Aloe vera extract containing Carbopol 934 as gelling agent and to investigate the effects of topical application of Carbopol 934 gel containing Aloe vera extract on the healing of skin wounds surgically induced in Wistar rats.

MATERIALS AND METHODS: Different concentrations of viscosity enhancer Carbopol 934 were tried and finally gel that showed good spreadability and consistency was selected for wound healing property of herbal gel of Aloe vera. Excision wound model was used for the study.

RESULTS: The optimized gel was evaluated for different physicochemical properties and wound healing property. Differences in wound healing were observed between the various treatments when compared to the control group. Tissue hyperplasia was lower in the control group compared to the other treated groups. In animals group treated with gel, 80.14% healing was observed up to 14(th) day. While in untreated group I (control) animals showed 52.68% healing of wounds on 14(th) day. On the other hand, control group animals also showed inflammation and pus formation up to 5(th) day of study, while treated animals did not showed any observable inflammation and pus formation.

CONCLUSION: Results shows prepared gel has promising effect on the wound healing process.

Chemical constituents of *Aloe barbadensis* Miller and their inhibitory effects on phosphodiesterase-4D

ABSTRACT

Aloe barbadensis Mill has been used as food and medicine for a long time. In order to investigate the chemical constituents of *A. barbadensis* and their inhibitory activities towards phosphodiesterase-4D (PDE4D), 70% methanol extract of the dried *A. barbadensis* powder was employed. Phytochemical investigation has led to the isolation of three new chromones, 5-(hydroxymethyl)-7-methoxy-2-methylchromone (4), 5-((4E)-2'-oxo-pentenyl)-2-hydroxymethylchromone (6), and 7-hydroxy-5-(hydroxymethyl)-2-methylchromone (7), together

with eighteen known compounds. Their chemical structures were determined based on spectroscopic methods including UV, IR, 1D and 2D NMR, and HRMS spectrometry. In addition, their inhibition against PDE4D was evaluated using tritium-labeled adenosine 3',5'-cyclic monophosphate ((3) H-cAMP) as the substrate. Inhibition was calculated by the variation of radioactivity after the reaction, and compounds 1-4, 10, and 21 exhibited certain inhibitory activities towards PDE4D, which can provide an explanation why *A. barbadensis* can serve as anti-inflammatory agents.

Aloe vera downregulates LPS-induced inflammatory cytokine production and expression of NLRP3 inflammasome in human macrophages

ABSTRACT

Aloe vera has been used in traditional herbal medicine as an immunomodulatory agent inducing anti-inflammatory effects. However, its role on the IL-1β inflammatory cytokine production has not been studied. IL-1β production is strictly regulated both at transcriptional and posttranslational levels through the activity of Nlrp3 inflammasome. In this study we aimed to determine the effect of Aloe vera on the molecular mechanisms of Nlrp3 inflammasome-mediated IL-1β production in LPS-activated human THP-1 cells and monocyte-derived macrophages. Our results show that Aloe vera significantly reduced IL-8, TNFα, IL-6 and IL-1β cytokine production in a dose dependent manner. The inhibitory effect was substantially more pronounced in the primary cells. We found that Aloe vera inhibited the expression of pro-IL-1β, Nlrp3, caspase-1 as well as that of the P2X7 receptor in the LPS-induced primary macrophages. Furthermore, LPS-induced activation of signaling pathways like NF-κB, p38, JNK and ERK were inhibited by Aloe vera in these cells. Altogether, we show for the first time that Aloe vera-mediated strong reduction of IL-1β appears to be the consequence of the reduced expression of both pro-IL-1β as well as Nlrp3 inflammasome components via suppressing specific signal transduction pathways. Furthermore, we show that the expression of the ATP sensor P2X7 receptor is also downregulated by Aloe vera that could also contribute to the attenuated IL-1β cytokine secretion. These results may provide a new therapeutic approach to regulate inflammasome-mediated responses.

Effects of Japanese traditional herbal medicines (Kampo) on growth and virulence properties of *Porphyromonas gingivalis* and viability of oral epithelial cells

ABSTRACT

CONTEXT: Kampos, commonly used in Japanese traditional medicine, are standardized herbal mixtures that have been used for centuries to treat a variety of ailments. We hypothesized that Kampos may have unidentified properties that may be beneficial in periodontitis, an inflammatory disease affecting the tooth-supporting tissues.

OBJECTIVE: The aim of our study was to investigate various Kampos and their natural ingredients for their effects on *Porphyromonas gingivalis* growth, adherence to epithelial cells and proteinase activity. In addition, their effects on oral epithelial cell viability were evaluated.

MATERIALS AND METHODS: Growth inhibition of *P. gingivalis* by various Kampos and their natural ingredients was evaluated by a microdilution broth assay method. Their effects on *P. gingivalis* proteinase activity and adherence to oral epithelial cells were determined by fluorometric assays. The cytotoxicity of test compounds towards oral epithelial cells was evaluated by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] test.

RESULTS: Of the 27 Kampos tested, 7 were found to inhibit the growth of *P. gingivalis*. The lowest minimal inhibitory concentration (MIC) (250 μg/ml) was obtained with TJ-113. Analysis of the composition of the seven active Kampos showed that they contain Chinese rhubarb as a common ingredient. Therefore, additional growth inhibitory assays on *P. gingivalis* were carried out with purified anthraquinones known to be present in rhubarb. Aloe-emodin and rhein possessed the strongest antibacterial effects towards *P. gingivalis* with an MIC of 0.78 μg/ml. The seven Kampos containing rhubarb and purified anthraquinones also exhibited the capacity to decrease the adherence of *P. gingivalis* to oral epithelial cells and to reduce its proteinase activity. The most important anti-adherence effect of Kampo was obtained with TJ-126; at 250 μg/ml it reduced adherence of *P. gingivalis* to epithelial cells by 83%. Purified anthraquinones were found to be less active than Kampos. Kampo TJ-113 was found to be the most effective for inhibition of gelatin degradation (49% inhibition at 62.5 μg/ml). Again, purified anthraquinones inhibited gelatin degradation to a lesser extent. Lastly, none of the tested compounds showed cytotoxicity towards oral epithelial cells at the effective concentrations.

CONCLUSION: Kampos containing rhubarb and its anthraquinone derivatives may represent promising molecules for controlling periodontal diseases through their capacity to inhibit *P. gingivalis* growth and virulence properties.

Facile synthesis of hierarchically aloe-like gold micro/nanostructures for ultrasensitive DNA recognition

ABSTRACT

Well-defined hierarchically aloe-like gold micro/nanostructures (HAG) are one-step electrochemically fabricated without introducing any template or surfactant. The formation kinetics of the HAG can be described as a nucleation and three-dimensional growth process controlled by the reactant diffusion from the

solution side. As the applied electro-deposition potential moved in the negative direction, the gold crystal density increased, and the crystal shape changed from a quasi-spherical to dendritic fractal morphology. Under the optimal potential of -0.1 V and the time of 10 min, well-defined HAG possessing a hydrophilic surface with large effective area (ca. 8 times of its geometrical area) were obtained, which was used as the substrate for fabricating an ultrasensitive DNA biosensor. The DNA biosensor displayed a significantly enhanced detection limit of 12 aM, a wide linear response from 50 aM to 1 pM, as well as good selectivity, stability and reusability. This efficient DNA molecule immobilization platform may have implications in the preparation of many other gold micro/nanostructures (GMNs) with interesting properties and application potentials in many fields, such as biosensing, biocatalysis and biofuel cells.

Aloe vera improves memory and reduces depression in mice

ABSTRACT

OBJECTIVE: *Aloe vera* (barbadensis Mill., Family Liliaceae) since ancient times has been used for the treatment of skin disorders, infection, and as a laxative. The present study was undertaken to explore the effect of *A. vera* (Family Liliaceae) in animal models of learning and memory, depression, and locomotion.

METHODS: To assess learning and memory, the passive avoidance task and elevated plus-maze were used. For evaluating depression, the forced swim test and tail suspension test were performed, and to assess locomotor activity, the rota rod test and photoactometer were used.

RESULTS: *A. vera* (200 and 400 mg/kg, p.o.) was found to significantly increase the acquisition and retention step-down latency as compared to control in the passive avoidance task. In the elevated plus-maze, the highest administered dose (400 mg/kg, p.o.) of *A. vera* significantly reduced the transfer latency as compared to control. The forced swim test as well as tail suspension test showed that *A. vera* at all administered doses (100, 200, and 400 mg/kg, p.o.) decreased the period of immobility significantly. However, the locomotor activity did not show any significant change in the rota rod test and photoactometer.

DISCUSSION: Thus from the above observations, it can be proposed that *A. vera* enhances learning and memory, and also alleviates depression in mice.

The co-use of conventional drugs and herbs among patients in Norwegian general practice: a cross-sectional study

ABSTRACT

BACKGROUND: Different patient groups are known to use herbal remedies and conventional drugs concomitantly (co-use). This poses a potential risk of herb-drug interaction through altering the drug's pharmacokinetics or pharmacodynamics. Little is known about co-use among patients in general practice. The primary aim of this study was to compare patients in general practice that co-use herbal remedies and conventional drugs with those who do not. The secondary aim was to register the herb-drug combinations with potential clinical relevant interactions among the co-users.

METHOD: A questionnaire based cross-sectional study conducted in the autumn 2011 in a general practice office with four general practitioners (GPs) and one intern in Western Norway. Adults >18 years who came for an office visit were invited. The questionnaire asked about demographics, herbal use, conventional drug use and communication about herbal use. Multivariable logistic regression was used to compare co-users to the other patients.

RESULTS: Of the 381 patients who completed the questionnaire, the prevalence of herbal use was 43%, with bilberry (41%), green tea (31%), garlic (27%), Aloe vera (26%) and echinacea (18%) as the most frequently used. Among those using conventional drugs regularly, 108 (45%) co-used herbs. Close to 40% of patients on anticoagulants co-used herbs, with garlic and bilberry as the most frequent herbs. Compared to all other patients, co-users had significantly ($p < 0.05$) increased odds to be female (adjOR 2.0), age above 70 years (adjOR 3.3), use herbs to treat an illness (adjOR 4.2), use two or more herbs (polyherbacy, adjOR 12.1) and having experienced adverse effects of herbal use (adjOR 37.5). Co-use was also associated with use of analgesics or dermatological drugs (adjOR 5.1 and 7.9 respectively). Three out of four patients did not discuss herbal use with any health care professional.

CONCLUSION: A sizable proportion of the GP patients co-used herbs with conventional drugs, also combinations with reported interaction potential or additive effects like anticoagulants and garlic. The low disclosure of herbal use to their GP, polyherbacy and the risk of interactions in vulnerable groups like elderly and chronically ill patients, warrant increased awareness among GPs.

Application of an efficient strategy based on liquid-liquid extraction, high-speed counter-current chromatography, and preparative HPLC for the rapid enrichment, separation, and purification of four anthraquinones from *Rheum tanguticum*

ABSTRACT

This study presents an efficient strategy based on liquid-liquid extraction, high-speed counter-current chromatography, and preparative HPLC for the rapid enrichment, separation, and purification of four anthraquinones from *Rheum tanguticum*.

A new solvent system composed of petroleum ether/ethyl acetate/water (4:2:1, v/v/v) was developed for the liquid-liquid extraction of the crude extract from R. tanguticum. As a result, emodin, aloe-emodin, physcion, and chrysophanol were greatly enriched in the organic layer. In addition, an efficient method was successfully established to separate and purify the above anthraquinones by high-speed counter-current chromatography and preparative HPLC. This study supplies a new alternative method for the rapid enrichment, separation, and purification of emodin, aloe-emodin, physcione, and chrysophanol. This article is protected by copyright. All rights reserved.

Clinical efficacy of new aloe vera- and myrrh-based oral mucoadhesive gels in the management of minor recurrent aphthous stomatitis: a randomized, double-blind, vehicle-controlled study

ABSTRACT

OBJECTIVE: To evaluate the clinical efficacy, and safety of newly customized natural oral mucoadhesive gels, containing either aloe vera or myrrh as active ingredients, in the management of minor recurrent aphthous stomatitis (MiRAS).

SUBJECTS AND METHODS: Ninety subjects with MiRAS were recruited from Oral Medicine Clinic, at Faculty of Dentistry, King Abdulaziz University, Saudi Arabia, for this randomized, double-blind, placebo-controlled study. Two new natural gels, containing aloe vera and myrrh, were prepared in a concentration of (0.5% w/w), in addition to a plain mucoadhesive gel used as a placebo. Patients with fresh ulcers (<48-h duration) were instructed to apply either one of the three gels four times a day for a period of 5 days. Clinical efficacy was investigated in the form of changes in ulcer size, pain intensity, erythema, and exudation at days 4 and 6 of study entry. Participants were interviewed for the emergence of any side effects.

RESULTS: 76.6% of patients using aloe gel showed complete ulcer healing, 86.7%, and 80% of them revealed subsidence of erythema and exudation, respectively, especially at day 6 visit, whereas 76.7% of myrrh-treated patients revealed almost absence of pain at day 6. No side effects were encountered with the use of any of the three gels.

CONCLUSION: The new formulated aloe- and myrrh-based gels proved to be effective in topical management of MiRAS. Aloe was superior in decreasing ulcer size, erythema, and exudation; whereas myrrh resulted in more pain reduction.

Pharmacokinetics of anthraquinones in rat plasma after oral administration of a rhubarb extract

ABSTRACT

A sensitive and specific LC-MS/MS method was developed for simultaneous determination of aloe-emodin, rhein, emodin, chrysophanol and physcion and their conjugates in rat plasma. The lower limit of quantitation of each anthraquinone was 0.020-0.040 μm. Intra-day and inter-day accuracies were 90.1-114.3% and the precisions were <14.6%. The matrix effects were 104.0-113.2%. The method was successfully applied to a pharmacokinetic study in rats receiving a rhubarb extract orally. The area under the concentration-time curve (AUC_{0-t}) and peak concentration (C_{max}) of free aloe-emodin and emodin in rat plasma were much lower than those of rhein. The amounts of chrysophanol and physcion were too low to be continuously detected. After treating the plasma samples with β-glucuronidases, each anthraquinone was detectable throughout the experimental period (36 h) and showed much higher plasma concentrations and AUC_{0-t}. The free/total ratios of aloe-emodin, rhein and emodin were 6.5, 49.0 and 1.7% for C_{max} and 3.7, 32.5 and 1.1% for AUC_{0-t}, respectively. The dose-normalized AUC_{0-t} and C_{max} of the total of each anthraquinone were in the same descending order: rhein > emodin > chrysophanol > physcion > aloe-emodin. These findings reveal phase II conjugates as the dominant in vivo existing forms of rhubarb antharquinones and warrant a further study to evaluate their contribution to the herbal activity.

Complementary and alternative medicine use in patients with chronic lymphocytic leukemia: an Italian multicentric survey

ABSTRACT

Complementary and alternative medicine (CAM) is common in patients with cancer and its use is steadily increasing over time. We performed a multicenter survey in which the use of CAM in 442 Italian patients with chronic lymphocytic leukemia (CLL), the commonest form of leukemia in Western countries, was assessed. Data were collected by means of a face-to-face standardized questionnaire with several items. Mean age was 69 years; 258 patients (58%) were male and 184 (42%) female. Seventy-three patients (16.5%) were found to be CAM users. The most common CAM therapies were green tea, aloe formulations and high dose vitamins. Predictors of CAM use were female gender, younger age, higher education level, internet availability and newspaper reading. The reasons for CAM popularity among these patients are complex. Given the number of patients combining therapy with CAM and its possible drug interactions, doctor interest as well as patient education about CAM should be improved.

Effect of crosslinking in chitosan/aloe vera-based membranes for biomedical applications

ABSTRACT

The positive interaction between polysaccharides with active phytochemicals found in medicinal plants may represent a strategy to create active wound dressing materials useful for skin repair. In the present work, blended membranes composed

of chitosan (Cht) and aloe vera gel were prepared through the solvent casting, and were crosslinked with genipin to improve their properties. Topography, swelling, wettability, mechanical properties and *in vitro* cellular response of the membranes were investigated. With the incorporation of aloe vera gel into chitosan solution, the developed chitosan/aloe-based membranes displayed increased roughness and wettability; while the genipin crosslinking promoted the formation of stiffer membranes in comparison to those of the non-modified membranes. Moreover, *in vitro* cell culture studies evidenced that the L929 cells have high cell viability, confirmed by MTS test and calcein-AM staining. The findings suggested that both blend compositions and crosslinking affected the physico-chemical properties and cellular behavior of the developed membranes.

Influence of Aloe vera on water absorption and enzymatic in vitro degradation of alginate hydrogel films

ABSTRACT

This study investigates the influence of *Aloe vera* on water absorption and the in vitro degradation rate of *Aloe vera*-Ca-alginate hydrogel films, for wound healing and drug delivery applications. The influence of *A. vera* content (5%, 15% and 25%, v/v) on water absorption was evaluated by the incubation of the films into a 0.1 M HCl solution (pH 1.0), acetate buffer (pH 5.5) and simulated body fluid solution (pH 7.4) during 24h. Results show that the water absorption is significantly higher for films containing high *A. vera* contents (15% and 25%), while no significant differences are observed between the alginate neat film and the film with 5% of *A. vera*. The *in vitro* enzymatic degradation tests indicate that an increase in the *A. vera* content significantly enhances the degradation rate of the films. Control films, incubated in a simulated body fluid solution without enzymes, are resistant to the hydrolytic degradation, exhibiting reduced weight loss and maintaining its structural integrity. Results also show that the water absorption and the *in vitro* degradation rate of the films can be tailored by changing the *A. vera* content.

In vitro evaluation of the cytotoxic and apoptogenic properties of aloe whole leaf and gel materials

ABSTRACT

Aloe gel and whole-leaf materials have shown biological effects with potential therapeutic applications, and recently, their drug-absorption enhancement properties have been discovered. It is important to establish a safety profile for these materials before they can be used in pharmaceutical products. The aim of the study was to investigate the *in vitro* cytotoxicity of *Aloe vera*, *Aloe marlothii*, *Aloe speciosa* and *Aloe ferox* against human hepatocellular (HepG2), human neuroblastoma cells (SH-SY5Y) and human adenocarcinoma epithelial cells (HeLa). Flow cytometry was used to measure cell viability, apoptosis and reactive oxygen species (ROS). The aloe gel materials investigated only decreased cell viability at concentrations of >10 mg/mL and exhibited half-maximal cytotoxic concentration (CC_{50}) values above 1000 mg/mL, except for *A. vera* gel in HepG2 cells (CC_{50} = 269.3 mg/mL). A. *speciosa* whole-leaf material showed a significant decrease in viability of Hela cells, whereas the other whole-leaf materials did not show a similar effect. The aloe gel materials in general showed low levels of apoptosis, whereas *A. vera* and *A. speciosa* whole-leaf materials caused a dose-dependent increase of apoptosis in HeLa cells. None of the aloe materials investigated exhibited a significant increase in ROS. It can be concluded that the selected aloe materials caused only limited reduction in cell viability with limited *in vitro* cytotoxicity effects. Further, neither significant apoptosis effects were observed nor induction of ROS.

Factors affecting xylene-contaminated air removal by the ornamental plant *Zamioculcas zamiifolia*

ABSTRACT

Fifteen plant species-*Alternanthera bettzickiana*, *Drimiopsis botryoides*, *Aloe vera*, *Chlorophytum comosum*, *Aglaonema commutatum*, *Cordyline fruticosa*, *Philodendron martianum*, *Sansevieria hyacinthoides*, *Aglaonema rotundum*, *Fittonia albivenis*, *Muehlenbeckia platyclada*, *Tradescantia spathacea*, *Guzmania lingulata*, *Zamioculcas zamiifolia*, and *Cyperus alternifolius*-were evaluated for the removal efficiency of xylene from contaminated air. Among the test plants, *Z. zamiifolia* showed the highest xylene removal efficiency. Xylene was toxic to *Z. zamiifolia* with an LC_{50} of 3,464 ppm. Higher concentrations of xylene exhibited damage symptoms, including leaf tips turning yellow, holonecrosis, and hydrosis. TEM images showed that a low concentration of xylene vapors caused minor changes in the chloroplast, while a high concentration caused swollen chloroplasts and damage. The effect of photosynthetic types on xylene removal efficiency suggests that a mixture of *Z. zamiifolia*, *S. hyacinthoides*, and *A. commutatum* which represent facultative CAM, CAM, and C_3 plants, is the most suitable system for xylene removal. Therefore, for maximum improvement in removing xylene volatile compounds under various conditions, multiple species are needed. The effect of a plant's total leaf area on xylene removal indicates that at lower concentrations of xylene, a small leaf area might be as efficient as a large leaf area.

Systematic review: the efficacy of herbal therapy in inflammatory bowel disease

ABSTRACT

BACKGROUND: Complementary and alternative medicine (CAM), particularly herbal therapy, is widely used by patients with inflammatory bowel disease (IBD) but controlled data are

limited.

AIM: To systematically review the literature on the efficacy of herbal therapy in the treatment of ulcerative colitis (UC) and Crohn's disease (CD).

METHODS: Publications in English and non-English literatures (MEDLINE, EMBASE, EBM Reviews, AMED, Global Health) were searched from 1947 to 2013 for controlled clinical studies of herbal therapy in IBD. Outcome measures included response and remission rates.

RESULTS: Twenty-one randomised controlled trials (14 UC; 7 CD) including a total of 1484 subjects (mean age 41, 50% female) were analysed. In UC, aloe vera gel, *Triticum aestivum* (wheat grass juice), *Andrographis paniculata* extract (HMPL-004) and topical Xilei-san were superior to placebo in inducing remission or response, and curcumin was superior to placebo in maintaining remission; *Boswellia serrata* gum resin and *Plantago ovata* seeds were as effective as mesalazine, whereas *Oenothera biennis* (evening primrose oil) had similar relapse rates as omega-3 fatty acids in the treatment of UC. In CD, *Artemisia absinthium* (wormwood) and *Tripterygium wilfordii* were superior to placebo in inducing remission, and preventing clinical recurrence of post-operative CD respectively.

CONCLUSIONS: Randomized controlled trials of herbal therapy for the treatment of IBD show encouraging results but studies remain limited and heterogenous. Larger controlled studies with stricter endpoints and better-defined patient groups are required to obtain more conclusive results on the use of CAM therapies in IBD.

Plant extracts for the topical management of psoriasis: a systematic review and meta-analysis

ABSTRACT

Patients with psoriasis frequently use preparations of plant extracts. Physicians need to be aware of the current evidence concerning these products. This review evaluates the efficacy and safety of preparations of plant extracts used topically for psoriasis. Searches were conducted in PubMed, Embase, the Cochrane library, two Chinese databases and article reference lists. Randomized controlled trials investigating extracts of single plants were included. Preparations of multiple plants and combinations of plant extracts plus conventional therapies were excluded. Two authors conducted searches, extracted data and assessed risk of bias. Outcomes used in meta-analyses were: clinical efficacy, Psoriasis Area and Severity Index score, and quality of life and symptom scores. The 12 included studies investigated extracts of: *Mahonia aquifolium* (n = 5), *Aloe vera* (n = 3), indigo naturalis (n = 2), kukui nut oil (n = 1) and *Camptotheca acuminata* nut (n = 1). Methodological quality was variable. Six studies provided data suitable for meta-analysis of clinical efficacy, and five were vs. placebo (relative risk 3·37, 95% confidence interval 1·36-8·33). Experimental studies indicate components of indigo naturalis, Mahonia and Camptotheca have anti-inflammatory, antiproliferative and other actions of relevance to psoriasis. The clinical trial evidence provides limited support for preparations containing extracts of *M. aquifolium*, indigo naturalis and *Aloe vera* for the topical management of plaque psoriasis based on multiple studies. No serious adverse events were reported. Because of the small size of most studies and methodological weaknesses, strong conclusions cannot be made. The magnitudes of any effects cannot be measured with accuracy, so it is difficult to assess the clinical relevance of these preparations.

Indan-C60: from a crystalline molecule to photovoltaic application

ABSTRACT

Crystalline Indan-C60 and its photovoltaic application were studied. Microsheets and aloe-like micro-nano superstructures can be assembled from Indan-C60. Indan-PC61BM derived from Indan-C60 was further investigated as an acceptor for OPV devices, which shows a higher Voc, FF, and PCE than those obtained using PC61BM.

In vivo synthesis of calcium oxalate whiskers on CoCrMo alloy surfaces via biomineralization

ABSTRACT

Surface treatments using bio-technology are valuable and fascinating in the sense that such treatments are natural and yield good biocompatibility. Calcium oxalate whiskers for biomedical applications were successfully synthesized on the CoCrMo alloy surfaces implanted in Aloe leaves which consist of many active bio-chemical elements. The effect of surface wettability and surface morphology on the formation of whiskers was investigated using four differently treated CoCrMo surfaces: (i) smoothly polished surface, (ii) electrochemical etched surface, (ii) textured surface with dimples, and (iv) parallel orientated-grooved surface. Results showed that the formed whiskers had a length ranging between 100 μm and 600 μm, and a diameter in the range of 2 μm to 5 μm. Electrochemically etched surfaces had better wettability and were favorably for growing whiskers. Surface morphology with (i) dimple textures or (ii) parallel grooves facilitated the effective control of the size and amount of the grown whiskers.

Modulation of drug efflux by aloe materials: An *In Vitro* investigation across rat intestinal tissue

ABSTRACT

BACKGROUND: Clinically, significant herb-drug interactions have been previously documented and can be pharmacodynamic and/or pharmacokinetic in nature. Pharmacokinetic interactions have been attributed to induction or inhibition of

either metabolic enzymes or efflux transporters.

OBJECTIVE: The effect of gel and whole leaf materials from 3 different aloe species namely *Aloe ferox*, *Aloe marlothii*, and *Aloe vera* as well as polysaccharides precipitated from the A. vera materials on the bi-directional transport of cimetidine across rat intestinal tissue was investigated.

MATERIALS AND METHODS: Cimetidine transport studies were performed across excised rat intestinal tissue mounted in Sweetana-Grass diffusion chambers in both the apical-to-basolateral and basolateral-to-apical directions.

RESULTS: While *A. vera* gel and whole leaf materials did not inhibit the efflux of cimetidine, the polysaccharides precipitated from them did show a reduction of cimetidine efflux. On the other hand, both *A. ferox* and *A. marlothii* gel and whole leaf materials exhibited an inhibition effect on cimetidine efflux.

CONCLUSIONS: This study identified a modulation effect of efflux transporters by certain aloe materials. This may cause herb-drug pharmacokinetic interactions when drugs that are substrates for these efflux transporters are taken simultaneously with aloe materials. On the other hand, these aloe materials may be used for drug absorption enhancement for drugs with low bioavailability due to extensive efflux.

Comparative pharmacokinetics of five rhubarb anthraquinones in normal and thrombotic focal cerebral ischemia-induced rats

ABSTRACT

A comparative oral pharmacokinetic study of five anthraquinones (aloe-emodin, emodin, rhein, chrysophanol and physcion) from the extract of Rheum palmatum L. was performed in normal and thrombotic focal cerebral ischemia (TFCI)-induced rats. The plasma samples were clarified through solid phase extraction prior to simultaneous determination of the anthraquinones with a validated high-performance liquid chromatography -fluorescence system. The results indicated that the Cmax , t1/2 and AUC0-t , of aloe-emodin, rhein, emodin and chrysophanol in TFCI-induced rats were nearly double, whereas the CL values were remarkably decreased ($p < 0.05$) over those of the normal rats. The plasma drug concentration-time data of five anthraquinones to rats fitted a two-compartment open model. The five anthraquinones in rat plasma were absorbed quickly and eliminated slowly in both groups. The obtained results could be helpful for evaluating the impact of the efficacy and safety of the drug in clinical applications. Copyright © 2012 John Wiley & Sons, Ltd.

Tes, Licuados, and Capsulas: Herbal Self-care Remedies of Latino/Hispanic Immigrants for Type 2 Diabetes

ABSTRACT

PURPOSE: The purpose of this cross-sectional, descriptive study was to explore the characteristics of herbal remedy use for diabetes among Latinos/Hispanics with type 2 diabetes.

METHOD: A convenience sample of 75 Latino/Hispanic adults with type 2 diabetes was recruited from community-based settings in North Carolina. Data were collected through face-to-face bilingual interviews. Measures included a demographic questionnaire; the Traditional, Complementary, and Alternative Practices Questionnaire; and biophysical indicators of A1C and body mass index.

RESULT: Sixty-nine percent of the sample reported using herbal remedies for diabetes self-care. Forty-nine herbal products were identified. The most commonly reported products were prickly pear cactus, aloe vera, celery, and chayote. The perceived effectiveness of products varied; some said they helped "a lot" while others noted the development of side effects. Over three quarters (77%) of persons using herbal remedies reported concurrent use with prescribed medications. Also, some participants reported skipping or altering the dose of diabetes medications when using herbal remedies. Most (77%) reported not disclosing herbal remedy use to health care providers.

CONCLUSION: Diabetes educators and other health care providers need to ask Latino/Hispanic clients about their use of herbal remedies and become knowledgeable about herbal products to provide advice about safety.

An integrated microfluidic platform for evaluating *in vivo* antimicrobial activity of natural compounds using a whole-animal infection model

ABSTRACT

The nematode *Caenorhabditis elegans* is a useful model host for pathogenesis research that can be infected by a large number of human pathogens. Conventionally, nematode-pathogen infection assays are mainly performed on agar medium which are labor-intensive and time-consuming. To overcome these challenges, we develop for the first time an integrated microfluidic device for evaluating *in vivo* antimicrobial activity of natural compounds, which allows infection and anti-infection assays to be sequentially and automatically carried out in liquid medium. The device consists of a worm dispenser with 32 trap-construction chambers and concentration gradient generators, in which the processes of introduction, dispensation, confinement of worms in the chamber and drug delivery to the chamber can be integrated into a single device. In addition, the operation of the device is simple and does not require any expensive robotic fluid handling systems to dispense samples. To demonstrate the ability of this device, we devise an on-line screening experiment using a *Caenorhabditis*

elegans-Staphylococcus aureus infection model and characterize the survival rate of the infected worms treated with antibiotics. Then, we applied the system to evaluate the antibacterial activity of several components of rhubarb: aloe-emodin, rhein and emodin at various concentrations. The device is able to load uniform worms into each chamber within 10 min and then generate various chemical concentrations automatically and simultaneously. Furthermore, the on-chip method only requires 6 h to establish the infection model and 48 h to perform the subsequent treatments. Based on the excellent advantages and scalable properties of microfluidics, the microfluidic platform holds a great potential in high-throughput screening for antimicrobials.

Natural ingredients in atopic dermatitis and other inflammatory skin disease

ABSTRACT

Active naturals in dermatology have been experiencing a renaissance. Many of the naturals that have been known for centuries to be effective for various skin conditions have now been scientifically validated with the unraveling of the pathophysiology behind their medicinal mechanism. This article seeks to present data on the clinical use of key dermatological active naturals such as oatmeal, feverfew, chamomile, aloe vera, licorice, and dexpanthenol, as well as on recent multicenter and international clinical studies that support their efficacy and safety profile for a variety of inflammatory skin conditions.

Metabolic effects of aloe vera gel complex in obese prediabetes and early non-treated diabetic patients: randomized controlled trial

ABSTRACT

OBJECTIVE: The metabolic effects of an aloe vera gel complex (Aloe QDM complex) on people with prediabetes or early diabetes mellitus (DM) are unknown. The goal of this study was to determine the effects of Aloe QDM complex on body weight, body fat mass (BFM), fasting blood glucose (FBG), fasting serum insulin, and Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR) in obese individuals with prediabetes or early DM who were not on diabetes medications.

METHODS: Participants (n = 136) were randomly assigned to an intervention or a control group and evaluated at baseline and at 4 and 8 wk.

RESULTS: The study lost six participants in the control group and eight in the intervention group. At 8 wk, body weight (P = 0.02) and BFM (P = 0.03) were significantly lower in the intervention group. At 4 wk, serum insulin level (P = 0.04) and HOMA-IR (P = 0.047) were lower in the intervention group; they also were lower at 8 wk but with borderline significance (P = 0.09; P = 0.08, respectively). At 8 wk, FBG tended to decrease in the intervention group (P = 0.02), but the between-group difference was not significant (P = 0.16).

CONCLUSION: In obese individuals with prediabetes or early untreated DM, Aloe QDM complex reduced body weight, BFM, and insulin resistance.

Monosaccharide analysis of succulent leaf tissue in Aloe

ABSTRACT

INTRODUCTION: The succulent leaf mesophyll in Aloe species supports a burgeoning natural products industry, particularly in Africa. Comparative data necessary to prioritise species with economic potential have been lacking.

OBJECTIVE: To survey leaf mesophyll monosaccharide composition in the genus Aloe using a predictive phylogenetic approach.

METHODOLOGY: Monosaccharide composition was assessed in 31 species, representing the morphological and taxonomic diversity of Aloe sensu stricto. Leaf mesophyll polysaccharides were partially hydrolysed in a trifluoroacetic acid (TFA)-SilA assay. Oximes and trimethylsilyl ether products were detected by GC-MS. Constituent monosaccharides accounting for the greatest variation among species were identified by principal component analysis. Two plant DNA barcoding regions were sequenced in 28 of the sampled species and the resulting maximum likelihood tree was used to evaluate phylogenetic signal in monosaccharide composition throughout the genus.

RESULTS: Nineteen peaks (Rt=16.76-23.67 min) were identified in the GC-MS spectra. All samples were dominated by one constituent; glucose was the major monosaccharide in 19 species, mannose in eight species, and xylose in one species (Aloidendron pillansii). Three monosaccharides therefore account for 90% of the variation in leaf mesophyll in Aloe. Species which do not share this typical monosaccharide profile appear to group outside the core Aloe clade in the phylogeny.

CONCLUSION: Preliminary findings suggest that leaf mesophyll monosaccharide composition is conservative in Aloe. Characterisation of within-species variation and quantitative differences between species will be necessary to authenticate leaf mesophyll products, whereas unusual monosaccharide profiles could be diagnostic in some species. The common glucose-mannose-xylose profile identified in commercially important species is shared by many other Aloe species.

Analysis of traditional knowledge in medicinal plants used by Yuan in Thailand

ABSTRACT

ETHNOPHARMACOLOGICAL RELEVANCE: We studied traditional knowledge of medicinal plants use of the Yuan in northern Thailand, documenting and analyzing tradi-

tional medical practices and its trend in the younger generations.

AIM OF THE STUDY: To providing useful information for appropriate and sustainable management under the urbanization and other developments and use of natural resources in their communities. In addition, traditional medicinal plant used, and knowledge that leads to discovery of new medicines can be promoted.

MATERIALS AND METHODS: Traditional medicinal plant knowledge of the Yuan in Lamphun province was studied from October 2009 through September 2011 in order to determine the important medicinal plant species and dominant use-categories in 5 villages. In each village, questionnaire interviews about medicinal plants uses were applied to 30 informants (5 informants per each of six stratified age groups). The relative importance of plant species was captured by calculation of use value (UV). Likewise, the dominant use-categories were determined by calculation of the informant agreement ratio (IAR). Correlations between informants' age and number of medicinal plants known by them were determined with the coefficient of determination (R(2)).

RESULTS: A total of 93 medicinal plant species in 82 genera and 49 families were recorded in the five villages. The most important species of medicinal plants were *Aloe vera* (L.) Burm.f., *Andrographis paniculata* Ness, *Chromolaena odorata* (L.) R.M.King and H.Rob., *Jatropha podagrica* Hook., and *Thunbergia laurifolia* Lindl. which had UVs of 1.02, 1.01, 0.75, 0.71, and 0.65, respectively. Likewise, the most dominant use-categories were injuries, which accounted for 0.91 of the IAR. The age of informants and medicinal plants reported by each of them were positively correlated ($R(2)=0.96$, $p<0.01$).

CONCLUSIONS: Most of the Yuan's traditional medicinal plant knowledge is used for treating basic ailments. However we should be concerned that there is an imminent danger that it will be lost in the near future because their lifestyle was changing.

Aluminium and other elements in selected herbal tea plant species and their infusions

ABSTRACT

The determination of Al, B, Cu, Fe, Mn, Ni, P, Zn and Ca, K, Mg by inductively coupled plasma optical emission spectrometry (ICP-OES) and flame atomic absorption spectroscopy (FAAS), respectively, in digests and infusions of *Hibiscus sabdariffa* (petals), *Rosa canina* (receptacles), *Ginkgo biloba* (leaves), *Cymbopogon citratus* (leaves), *Aloe vera* (leaves) and *Panax ginseng* (roots) was carried out in this study. Particular attention has been given to Al and heavy metals for the identification of possible raw material contaminants, their transformation into the infusion and for predicting their eventual role in the human diet during daily consumption. Additionally, Ion Chromatography (IC) speciation of Al in the leachates was carried out. In dry herbs, hibiscus and ginkgo appeared to contain the greatest contents of Al, Fe, K, Mn, Ni, Zn and B, Mg, P, respectively. A. vera contained the highest amount of Ca and highest values of Cu and P were observed in ginseng. In infusions, the topmost concentrations of Al, B, Cu, Fe, P, K, Mn, Ni, Zn were detected in those prepared from hibiscus petals, Ca from aloe leaves and Mg from leaves of ginkgo. According to a possible daily consumption exceeding 1 L, hibiscus decoction was identified as potentially dietetically significant in the content of certain elements. It seems to be possibly one of the top contributors of B from food (up to 5.5±0.2 mg/L). The Mg contained in the infusion (up to 106±5 mg/L) may be a contributor in the attenuation of blood pressure. A high amount of accessible Mn (up to 17.4±1.1 mg/L) can probably have an adverse effect in humans. The total Al allowance (up to 1.2±0.1 mg/L) suggests that no more than 1 L of the hibiscus infusion should be consumed per day by sensitive individuals including pregnant women and should be completely excluded from the diet of children under 6 months of age and children with chronic renal failure.

Preparation and characterization of aloe vera blended collagen-chitosan composite scaffold for tissue engineering applications

ABSTRACT

Collagen-Chitosan (COL-CS) scaffolds supplemented with different concentrations (0.1-0.5%) of aloe vera (AV) were prepared and tested in vitro for their possible application in tissue engineering. After studying the microstructure and mechanical properties of all the composite preparations, a 0.2% AV blended COL-CS scaffold was chosen for further studies. Scaffolds were examined by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and thermogravimetry analysis (TGA) to understand the intermolecular interactions and their influence on the thermal property of the complex composite. Swelling property in phosphate buffered saline (pH 7.4) and in vitro biodegradability by collagenase digestion method were monitored to assess the stability of the scaffold in a physiological medium in a hydrated condition, and to assay its resistance against enzymatic forces. The scanning electron microscope (SEM) image of the scaffold samples showed porous architecture with gradual change in their morphology and reduced tensile properties with increasing aloe vera concentration. The FTIR spectrum revealed the overlap of the AV absorption peak with the absorption peak of COL-CS. The inclusion of AV to COL-CS increased the thermal stability as well as hydrophilicity of the scaffolds. Cell culture studies on the scaffold showed enhanced growth and proliferation of fibroblasts

(3T3L1) without exhibiting any toxicity. Also, normal cell morphology and proliferation were observed by fluorescence microscopy and SEM. The rate of cell growth in the presence/absence of aloe vera in the scaffolds was in the order: COL-CS-AV > COL-CS > TCP (tissue culture polystyrene plate). These results suggested that the aloe vera gel-blended COL-CS scaffolds could be a promising candidate for tissue engineering applications.

A protein from *Aloe vera* that inhibits the cleavage of human fibrin(ogen) by plasmin

ABSTRACT

A protease inhibitor protein with the molecular mass of 11,804.931 Da (analyzed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) was isolated from *Aloe vera* leaf gel and designated as AVPI-12. The isoelectric point of the protein is about 7.43. The first ten amino acid sequence from the N-terminal was found to be R-D-W-A-E-P-N-D-G-Y, which did not match other protease inhibitors in database searches and other publications, indicating AVPI-12 is a novel protease inhibitor. The band protein of AVPI-12 migrated further on nonreducing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) than reducing SDS-PAGE. This result indicated that the molecule of AVPI-12 did not contain interchain disulfide bonds, but appeared to have intrachain disulfide bonds instead. AVPI-12 strongly resisted digestion by the serine proteases human plasmin and bovine trypsin. The protein could protect the γ-subunit of human fibrinogen from plasmin and trypsin digestion, similar to the natural plasma serine protease inhibitor α2-macroglobulin. The protein also could protect the γ-subunit of fibrinogen from the cysteine protease papain. AVPI-12 also exhibited dose-dependent inhibition of the fibrinogenolytic activity of plasmin, similar to α2-macroglobulin. The fibrinolytic inhibitory activity of AVPI-12 and the small-angle X-ray scattering showed that the protein could protect human fibrin clot from complete degradation by plasmin. The inhibition of the fibrinogenolytic and fibrinolytic activities of plasmin by AVPI-12 suggests that the inhibitor has potential for use in antifibrinolytic treatment.

UPLC-ESI/MS determination of 17 active constituents in two categorized formulas of traditional Chinese medicine, Sanhuang Xiexin Tang and Fuzi Xiexin Tang: application in comparing the differences in decoctions and macerations

ABSTRACT

A rapid and sensitive UPLC-ESI/MS method was established and validated to determine 17 active constituents (aconitine, hypaconitine, mesaconitine, benzoylaconine, benzoylhypaconine, benzoylmesaconine, berberine, palmatine, jatrorrhizine, coptisine, baicalein, wogonin, baicalin, wogonoside, emodin, aloe-emodin and rhein) in Sanhuang Xiexin Tang (SXT) and Fuzi Xiexin Tang (FXT), which are two classic compound recipes from Xiexin Tang categorized formulas in traditional Chinese medicien. The separation was performed on a UPLC BEH C18 column gradient eluted using acetonitrile and 0.1% formic acid as mobile phase. ESI/MS was operated in positive ([M + H](+)) in selected ion recording mode for analysis of alkaloids and flavones, while in negative ([M - H](-)) selected ion recording mode for anthraquinones. All of the 17 constituents exhibited good linearity in a relatively wide concentration ranges with the lowest limits of detection of 0.38 ng/mL. All of the relative standard deviation values of intra- and inter-precisions and stabilities of 17 constituents were within 5%. The method was successfully applied to determine 17 active constituents in decoctions and macerations of SXT and FXT. The results indicated that different preparative methods resulted in significant diversity in concentrations of the 17 analytes. Herb-herb interaction appeared between aconitum alkaloids in Aconiti Lateralis Radix Preparata and another three herbs.

Extraction and purification of anthraquinones derivatives from *Aloe vera* L. using alcohol/salt aqueous two-phase system

ABSTRACT

An alcohol/salt aqueous two-phase system (ATPS) composed of 1-propanol and (NH4)2SO4 was employed to purify anthraquinones (AQs) extracted from Aloe vera L. The main influencing system parameters such as type of alcohol, type and concentration of salt, temperature and pH were investigated in detail. Under the optimal extraction conditions, AQs can be extracted into alcohol-rich phase with high extraction efficiency, meanwhile majority polysaccharides, proteins, mineral substances and other impurities were extracted into salt-rich phase. Partitioning of AQs is dependent on hydrophobic interaction, hydrogen bond interaction, and salting-out effect in ATPS. Temperature also played a great role in the partitioning. After ATPS extraction, alcohol can be recycled by evaporation; moreover, salt can be recycled by dilution crystallization method. Compared with other liquid-liquid extractions, this alcohol/salt system is much simpler, lower in cost with easier recovery of phase-forming components, which has the potential scale-up in down-processing of active ingredients in plant.

Aloe vera for prevention of radiation-induced dermatitis: a self-controlled clinical trial

ABSTRACT

To evaluate an *Aloe vera* lotion for prevention of radiation-induced dermatitis, all patients with a prescription of radiotherapy to a minimum dose of 40 Gy were eligible provided that their treatment area could be divided into two symmetrical halves. Patients were given a lotion of *Aloe vera* to use on

one half of the irradiated area, with no medication to be used on the other half. The grade of dermatitis in each half was recorded weekly until 4 weeks after the end of radiotherapy. The trial enrolled 60 patients (mean age: 52 years; 67% women). Most patients had breast cancer (38%), followed by pelvic (32%), head-and-neck (22%), and other cancers (8%). Field size was 80-320 cm(2) (mean: 177 cm(2)), and the dose of radiotherapy was 40-70 Gy (mean: 54 Gy). Concurrent chemotherapy was administered in 20 patients. From week 4 to week 6 of radiotherapy and then at weeks 2 and 4 after radiotherapy, the mean grade of dermatitis with and without *Aloe vera* was 0.81 and 1.10 ($p < 0.001$), 0.96 and 1.28 ($p < 0.001$), 1.00 and 1.57 ($p = 0.006$), 0.59 and 0.79 ($p = 0.003$), and 0.05 and 0.21 ($p = 0.002$) respectively. Age and radiation field size had a significant effect on the grade of dermatitis. Based on these results, we conclude that the prophylactic use of *Aloe vera* reduces the intensity of radiation-induced dermatitis.

Dietary *Aloe vera* components' effects on cholesterol lowering and estrogenic responses in juvenile goldfish, *Carassius auratus*

ABSTRACT

Aloes are now considered a very interesting source of bioactive compounds among which phytosterols should play a major role. The present study is an attempt to investigate the hypocholesterolemic activity of *Aloe vera* associated with its impact on the reproductive status of juvenile goldfish. Therefore, the short- and long-term effects of feeding supplementary diet containing aloe components (20 mg aloe/g diet; 2%) on plasma lipids, plasma vitellogenin, and hepatic estrogen receptor α/β1 mRNA levels in goldfish were examined. Results of GC-MS for phytosterols show high abundance of β-sitosterol in freeze-dried powder of *Aloe vera* whole leaves. Moreover, a 2% aloe powder dietary supplement was not found estrogenic in juvenile goldfish after either 7- or 30-day treatment, but was consistent in plasma hypocholesterolemic effects following long-term exposure. The present data further support that plasma cholesterol modulation induced by phytosterols may not be related to estrogen-like activity.

Influence of *Aloe arborescens* Mill. extract on selected parameters of pro-oxidant-antioxidant equilibrium and cytokine synthesis in rowers.

ABSTRACT

This investigation examined the effect of supplementation with Biostimine, extract from *Aloe arborescens* Mill. leaves, on the levels of pro-oxidant-antioxidant equilibrium markers and anti- and proinflammatory cytokines in rowers subjected to exhaustive exercise. This double-blind study included 18 members of the Polish Rowing Team. Subjects were randomly assigned to the supplemented group (n = 9), which received one ampoule of Biostimine once daily for 4 weeks, or to the placebo group (n = 9). Subjects performed a 2,000-meter-maximum test on a rowing ergometer at the beginning and end of the preparatory camp. Blood samples were obtained from the antecubital vein before each exercise test, 1 min after completing the test and after a 24-hr recovery period. Superoxide dismutase and glutathione peroxidase activity as well as the concentration of thiobarbituric acid reactive substances (TBARS) were assessed in erythrocytes. In addition, total antioxidant capacity (TAC) and creatine kinase activity were measured in plasma samples, and cytokine (IL-6, IL-10) concentrations were determined in the serum. Before and after Biostimine supplementation, exercise significantly increased the values of SOD, IL-6, IL-10, and TBARS in both groups. However, postexercise and recovery levels of TBARS were significantly lower in athletes receiving Biostimine than in controls. After supplementation, TAC was the only variable with the level being significantly higher in the supplemented group than in the placebo group. Consequently, we can conclude that Biostimine supplementation reduces the postexercise level of TBARS by increasing the antioxidant activity of plasma but has no effect on inflammatory markers.

UP780, a chromone-enriched aloe composition improves insulin sensitivity

ABSTRACT

BACKGROUND: Diabetic individuals experience elevated fasting glucose, glycosylated hemoglobin (HbA1c), and plasma insulin and impaired glucose tolerance. Adiponectin is a hormone inversely correlated with insulin resistance. Here we describe the activity of aloesin, an aloe chromone that increases adiponectin production and, when formulated with an aloe polysaccharide composition, improves the insulin sensitivity in db/db and diet-induced obese-diabetic mice.

METHODS: Two aloe chromones, aloesin and aloesinol, were tested in vitro for adiponectin production. Following confirmation of glucose-lowering activity in a high-fat diet (HFD)-induced mouse model, aloesin was formulated with an Aloe vera inner leaf gel powder polysaccharide preparation to yield a composition designated UP780. Efficacy of UP780 was evaluated in HDF-induced and db/db mouse models. GW1929, a synthetic peroxisome proliferator-activated receptor-γ (PPARγ) agonist, was used as a positive control.

RESULTS: After 3 weeks of treatment of HDF-induced mice, plasma insulin levels were decreased 37.9% and 46.7% by aloesin and aloesinol, respectively. In db/db mice, the chromone- (2% chromone:98% aloe polysaccharide) enriched UP780 aloe composition showed a 33.7% and 46.0% decrease in fasting triglyceride and plasma glucose levels after 10 weeks of oral treatment, respectively. Diabetic mice gavaged with

200 mg/kg of UP780 for 10 weeks showed a 30.3% decrease in fasting blood glucose levels and a 32.2% reduction in plasma insulin. In both animal models, UP780 showed a statistically significant improvement in blood glucose clearance.

CONCLUSION: These findings indicate that UP780, a chromone-standardized, aloe-based composition, could potentially be used as a natural product option to facilitate the maintenance of healthy blood glucose levels.

Toxicology and carcinogenesis studies of a noncolorized whole leaf extract of *Aloe barbadensis* Miller (Aloe vera) in F344/N rats and B6C3F1 mice (drinking water study)

ABSTRACT

BACKGROUND: Extracts from the leaves of the *Aloe vera* plant (*Aloe barbadensis* Miller) have long been used as herbal remedies and are also now promoted as a dietary supplement, in liquid tonics, powders or tablets, as a laxative and to prevent a variety of illnesses. We studied the effects of *Aloe vera* extract on rats and mice to identify potential toxic or cancer-related hazards.

METHODS: We gave solutions of nondecolorized extracts of *Aloe vera* leaves in the drinking water to groups of rats and mice for 2 years. Groups of 48 rats received solutions containing 0.5%, 1% or 1.5% of Aloe vera extract in the drinking water, and groups of mice received solutions containing 1%, 2%, or 3% of Aloe vera extract. Similar groups of animals were given plain drinking water and served as the control groups. At the end of the study tissues from more than 40 sites were examined for every animal.

RESULTS: In all groups of rats and mice receiving the *Aloe vera* extract, the rates of hyperplasia in the large intestine were markedly increased compared to the control animals. There were also increases in hyperplasia in the small intestine in rats receiving the Aloe vera extract, increases in hyperplasia of the stomach in male and female rats and female mice receiving the *Aloe vera* extract, and increases in hyperplasia of the mesenteric lymph nodes in male and female rats and male mice receiving the *Aloe vera* extract. In addition, cancers of the large intestine occurred in male and female rats given the *Aloe vera* extract, though none had been seen in the control groups of rats for this and other studies at this laboratory.

CONCLUSION: We conclude that nondecolorized *Aloe vera* caused cancers of the large intestine in male and female rats and also caused hyperplasia of the large intestine, small intestine, stomach, and lymph nodes in male and female rats. *Aloe vera* extract also caused hyperplasia of the large intestine in male and female mice and hyperplasia of the mesenteric lymph node in male mice and hyperplasia of the stomach in female mice.

REGULATORY NEWS

FDA enforcement and the noncompliance risk profile

By Anthony Young Kleinfeld, Kaplan & Becker LLP and AHPA General Counsel

As we approach the 20th anniversary of the Dietary Supplement Health and Education Act of 1994 (DSHEA), it should be apparent to all that this is indeed a regulated industry. DSHEA and the Food and Drug Administration's (FDA) regulations set the standards for labels, claims, and current good manufacturing practices (cGMPs)—all of which draw a relatively tight circle around how supplements are manufactured, labeled, and marketed. Yet FDA warning letters only tell a piece of the supplement noncompliance risk profile. So if your risk analysis includes only FDA and you believe stopping unlawful claims once you've been warned is the cold shower of compliance, it's time to think more broadly.

You know that FDA publishes warning letters on its website and that readers include competitors, customers, and plaintiffs' lawyers eager to "enforce" regulatory requirements through lawsuits on behalf of allegedly misled consumers. From your bank account to theirs is more costly than simply stopping the alleged unlawful conduct.

Moreover, competitors and plaintiffs' lawyers may not be concerned about unlawful disease claims alone; they will probe the existence and nature of the substantiation you have for those claims. In short, these nongovernmental actors may dig deep below the surface of your products and how you sell them. Some state attorney general offices have learned that they can finance their operations with collections from cases brought against companies for false or misleading claims. This practice has been followed for some time in California.

Why are we telling you this? Because many of the actions we describe are not reported in the trade press and they certainly are not talked about with competitors. When was the last time a competitor admitted it had settled a threatened lawsuit or a state claim for high five figures?

And did you know that many state food and drug inspectors also "enforce" FDA dietary supplement labeling and cGMPs? These inspectors simply read FDA regulations and then write up violations, which can be followed by fines and penalties. Have you also noticed that state budgets are out of balance? This reality makes a violation an income source. And, of course, these violation reports are likely to swiftly end up in FDA files.

When you go to sell your brand or your company, the prospective buyers do what is called "due diligence." These buyers hire consultants and lawyers to evaluate whether you are in compliance with applicable regulations. If you are not, the information is used to either drop out of the competition to purchase or to reduce their offering price.

Complying with labeling requirements and claims regulations is not rocket science. Taking risks with claims has been a dietary supplement industry tradition, but the noncompliance risk profile has changed. Be mindful of the collateral consequences of noncompliance.

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FDA courtesy letters do not explain why claims are disease claims

By Anthony L. Young, Kleinfeld, Kaplan & Becker LLP and AHPA General Counsel

When a company makes a 30-day notification of a structure function claim to the Food and Drug Administration (FDA) (21 CFR 101.93), FDA reviews the claim to ascertain whether it is an appropriate structure function claim or whether it is a "disease" claim. If the FDA believes the claim is a disease claim, a "courtesy letter" is sent to the company that filed the notification. The courtesy letter identifies the product, the ingredients, and the claim and concludes that "the statement that you are making for this product suggests that it is intended to treat, prevent, or mitigate diseases" and that this does not comply with the structure function claim provision of the law.

Here are some ingredients and claims for which courtesy letters recently made public on Regulations.gov were sent to notify submitting companies:

- Glucosamine, chondroitin, MSM: helps promote cartilage regeneration
- No ingredients described: helps maintain joint flexibility, supports natural anti-inflammatory response, and natural anti-inflammatory support; may help lower blood sugar; may help lower blood pressure; healthy cholesterol levels; proven effective for its ... diuretic capabilities' lower cholesterol levels; pain relief; shortens the common cold; promote and replenish intestinal bacteria
- Omega-3: promotes key anti-inflammatory pathway
- Glucosamine and chondroitin: joint mobility
- Turmeric Curcumin extracts: supports a healthy inflammation response, inflammatory mediator 5-lipoxyginase, proinflammatory, supports a healthy inflammatory response and healthy range of motion in humans
- Maqui Berry: inflammatory response benefits
- Calcium: "may reduce their high risk of developing osteoporosis ..."; "... 10% risk of reduced fracture ..."
- Folate: "reduce ... risk of ... brain or spinal cord defect"
- Quercetin Nettle: supports healthy histamine release; healthy support inflammatory process
- Vitamin B12: insufficient amounts leads to pernicious anemia; reduce cholesterol levels
- Elderberry: support a healthy inflammatory response
- Boron: protects against excessive bone loss

When a courtesy letter is sent, FDA copies the district office where the company resides. This means that when the company is inspected, the investigator may ask what the company did after receiving the letter. A courtesy letter is just that. It is a large step below a warning letter which signals a volatile condition that FDA is willing to go to court, where the law is enforced, if compliance is not achieved.

Note that the courtesy letters do not explain in any way why, for example, the claim "joint mobility" is a disease claim. For those who are well aware of FDA's structure function claim regulation, its preamble and enforcement history, some of the claims above are recognizable as claims FDA has long objected to.

These courtesy letters provide an insight as to FDA's current conclusions regarding disease claims. They would be more transparent if they indicated FDA's current thinking, but they do not.

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