INNOVATIONS in pharmacy

Volume 8 | Number 2 Article 4

4-17-2017

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Novel Considerations about Diabetes Management Strategies in Chinese Immigrants in America: Possible Corollaries of the Use of Traditional Chinese Medicines

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Abstract
Worldwide, the prevalence of type 2 diabetes mellitus (T2DM) and its related management costs have increased over time. The latest predictions anticipate this trend to continue during the next few decades. As individuals with T2DM in the United States (US) are burdened with escalating prescription drug expenses, the appeal and use of cost effective alternatives may also increase. Herbal supplements are an example of such an alternative, but are unregulated and mostly lacking scientific evidence of advertised claims. In general, plant based herbal preparations are often advertised as 'natural', 'less-toxic', 'medicines' and are widely available from public retailers throughout the country. Over half of the US adult population report the use of supplements. Eastern countries, and especially China, have a long history of the use of herbal preparations as traditional medicine to prevent and treat diabetes. Recently the US has experienced a growth in the number imports of herbal supplements and other Traditional Chinese Medicines (TCM) to the country as well as the most rapid population growth in individuals who identify themselves as Asian. To date, little is known about the prevalence TCM use in the management of T2DM either alone or in combination with prescription medicines in the US. Knowledge of possible implications to patient safety (e.g., interactions, adverse effects) with concurrent use of both TCM and prescription medicines is also lacking. This review begins with summaries of the T2DM management strategies employed in traditional modern medicine (TMM) and Chinese medicine (TCM). A review of literature follows where the most commonly used TCM herbal preparations and their ingredients are identified and found along with any published reports of their proposed mechanisms of action, efficacy, adverse effects, and contraindications.

Keywords: Diabetes, America, Traditional Chinese Medicine, herbal supplements, dietary supplements, pharmacology

1.0 Diabetes: A Global Health Concern

Diabetes is one of the largest and rapidly progressing global health concerns of the modern day era [1, 2]. The International Diabetes Federations predicts the number of individuals between 20 and 79 years of age with diabetes to increase from 4.72 million in 2015 to 6.16 million by 2040 [2]. Being the most populous region of the world, China has the highest population of adults with diabetes, followed by India, and the United States (US) [2]. In China, the prevalence of adults with diabetes has risen approximately 10% since the late 1970s (i.e., from 0.67% to 11.6%) [3]. Even with lower rates of overall overweight and obesity, the Chinese and other individuals of Asian descent are particularly prone to develop diabetes earlier in life and at a lower BMI and waist circumference than European and Western individuals [4]. Such observations prompted the World Health Organization to redefine conventional definitions of overweight as BMI ≥ 25 kg m^2 and obesity BMI ≥ 35 kg m^2 to BMI ≥ 24 kg m^2 and BMI ≥ 28 kg m^2 in Asians [5, 6].

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Other risk factors attributable to diabetes predisposition in Asian populations include a possible genetic susceptibility as well as increases in 1) overall and abdominal obesity, 2) abdominal and visceral adiposity for a given BMI, 3) westernization of diet and lifestyle/urbanization and food supply, 4) over-nutrition, 5) sedentary behavior, 6) cigarette smoking, 7) pancreatic beta cell dysfunction, 8) low birth weight.

Beyond a considerable prevalence, the global economic burden of diabetes is also astounding. In 2015, the US led the world in diabetes related health care related expenditures at 320 billion USD (320 Billion ID) followed by China at 51 billion USD (90 billion ID) [2]. Since 1980, there has been fourfold increase in the number of Asians immigrating to the USA, the majority of which emigrated from China. Currently, the most recent Census data (2010) shows the Asian population grew over 40%, faster than any other race group, over the last decade with almost six percent of the US population now identifying as Asian either solely or in combination with one or more other races [7]. With health care insurance and related costs continuing to rise, it is possible that more individuals may seek more cost effective options to manage their disease. An easily accessible option in the US with cultural significance to a minority population experiencing the most rapid growth is Tradition Chinese Medicine (TCM).

2.0 Diabetes Management in Modern Medicine

Type 2 diabetes mellitus (T2DM), the most prevalent form of diabetes, is the result of insulin resistance and a progressive loss of insulin secretion. Once considered to be an ailment affecting only adults is now a worthy and concerning possibility in children and adolescents. This shift in representation is attributed to concomitant increases in obesity, diets lacking in fruit and vegetable consumption yet high in refined sugar, as well as increasing wealth, urbanization, physical inactivity, and changes in society and cultural norms [8].

2.1 Screening and Diagnosis

A number of risk factors for T2DM have been identified and are used to guide screening efforts in traditional modern medicine (TMM). They include but are not limited to obesity, a sedentary lifestyle, cigarette smoking, a family history of T2DM, prior gestational diabetes, evidence of abnormal glucose metabolism, or being of Asian, Hispanic, or African-American descent. Recommendations for screening exist to identify those at an increased risk of developing diabetes (i.e., prediabetes), as well as those with overt disease. Fortunately, the same tests are used for both screening and diagnosis. The routine screening of adults should begin at 45 years of age, regardless their body weight. As well, any overweight (i.e., BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adult regardless of age should also be screened. Screening methods involve either the measurement a fasting plasma glucose (FPG), glycosylated hemoglobin (HbA_{1C}), or else a two-hour 75g oral glucose tolerance test (OGTT),). Those with a FPG ≥126 mg/dL, an A_{1C} ≥6.5%, or a plasma glucose of ≥200 mg/dL at two hours during a 75g OGTT meet diagnostic criteria for diabetes, while those with values between 100-125 mg/dL, 140-199 mg/dL, and 5.7-6.4% respectively have impaired glucose tolerance, also referred to as prediabetic [9]. One other method of establishing a diagnosis of diabetes is based on the finding of a random plasma glucose ≥200mg/dL in an individual presenting with the classical symptoms of hyperglycemia [9]. Refer to Table 1 for a summary of diagnostic criteria.

2.2 Medical Management of Type II Diabetes Mellitus

Generally speaking, management consists of strategies to reduce hyperglycemia in order to prevent overt disease in those with impaired glucose tolerance, and complications in those with evidence of disease [10]. Effective glycemic control slows disease progression and significantly reduces the risk of long-term microvascular, macrovascular, and neuropathic complications (e.g., retinopathy, nephropathy, neuropathy, peripheral vascular, and coronary artery disease) [11, 12]. As such, at the time diagnosis it is necessary to establish a current estimation of micro and macrovascular disease state or baseline on which future comparisons to gauge the efficacy of treatments can be made. Assessments of an individual's cardiovascular risk factors, (i.e., smoking status, lipid profile, blood pressure), baseline renal function, diabetic foot examination, ophthalmological examination should be completed.

Subsequent management of T2DM in TMM necessitates individually tailored, multifactorial interventions involving a combination of approaches to self-management including educational, supportive, behavioral, nutritional, lifestyle, and pharmaceutical components. Standards of medical care in diabetes are published on an annual basis that contain recommendations for glycemic targets upon which estimates of treatment efficacy can be made [13]. Though not telling of hypoglycemic events or glycemic variability in general, HbA_{1C} does allow for estimation of the average blood glucose concentrations over the past several months and is predictive of diabetic related complications [14, 15]. The target HbA_{1C} indicative of glycemic control and a lower risk of diabetes related microvascular complications in adults in <7%. Additionally, blood glucose self-monitoring is also useful as a means of assessing glycemic control however the timing, frequency, and specific goals of monitoring needs vary between individuals as well as selected treatments.

2.2.1 Initial Strategies

In TMM, the mainstay of preventative measures in those with prediabetes as well as the initial treatment in those with T2DM is a focus on knowledge provision and intensive lifestyle modification with specific goals of weight loss as appropriate, medical nutritional therapy, and 150 minutes of moderately intensive physical activity per week. Intensive lifestyle modification is the initial management strategy used in modern medicine to reduce the prevalence of and initially manage T2DM [16-18]. Benefits of these types of interventions have been reported in group-based lifestyle interventions in both the residents of China as well as Chinese-speaking immigrants with prediabetes in the USA [16, 19]. The China Da Qing Diabetes Prevention Study found that the effects of a lifestyle intervention over a six-year span can prevent or delay diabetes for up to 14 years post-intervention. As well, those who participated in the intervention spent 3.6 fewer years with diabetes than those who did not [16]. A randomized controlled trial by Yeh et al. (2016) examined the feasibility and acceptability of a community based, intensive lifestyle modification program in a sample of Chinese-speaking immigrants with prediabetes in New York City. At 12 months post-intervention, intervention participants had lost significantly more weight and lower HbA_{1C}, BMI, body fat percentage, and waist circumference [19].

2.2.2. Pharmaceutical Strategies Used to Achieve Glycemic Control

As depicted in Figure 1, when intensive lifestyle modification fails to result in adequate glycemic control, antihyperglycemic pharmaceutical interventions are added to the management regime until effect control attained [13]. Typically, monotherapy is initiated with Metformin. Additional oral

hypoglycemic agents are subsequently added as needed when hyperglycemia persists after a three-month trial of a particular drug combination (i.e., 2-drug and 3-drug combinations). Should blood glucose levels remain refractory to a three-month trial of a 3-drug oral antihyperglycemic therapy, injectable antihyperglycemic therapies are used to achieve adequate control.

2.3 Medical Management of Type II Diabetes Mellitus Comorbidities

At the time of diagnosis, it essential to obtain baseline assessments for a number of comorbid conditions common in diabetic populations. These conditions typically involve micro and macrovascular predicaments that are often asymptomatic yet advanced at presentation and thus must be managed appropriately.

2.3.1 Atherosclerotic Cardiovascular Disease Cardiovascular Disease Risk Factors

Cardiovascular disease risk factors should be evaluated annually in T2DM. Careful risk factor management strategies such as smoking cessation, low dose aspirin therapy, as well as blood pressure and lipid regulation reduces the likelihood of cardiovascular events.

Hypertension

Blood pressure should be measured at every clinic visit and hypertension managed with a treatment goal of 130-139/70-89mmHg. Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) are the drug of choice because as they have been shown to slow the progression of renal disease in hypertensive patients with moderately increased albuminuria (formerly called microalbuminuria) [20]. Substitutions with an alternative class of antihypertensive medication should be when there is ACE-I or ARB intolerance, though it is likely that multiple drugs may be needed to adequately control blood pressure.

Lipid Management

Lipid management is also a key component of T2DM management (see Tables 2 and 3). The ADA suggests intensive lifestyle modifications to improve a patient's lipid profile such as optimization of glycemic control; weight loss if indicated; reducing intake of saturated fat, trans fat, and cholesterol; increase intake of omega-3 fatty acids, viscous fiber, and plant stanols or sterols; and increasing physical activity [13]. Statin therapies are the mainstay medical management and recommended for most individuals with diabetes who are forty years of age or older. Additional cardiovascular benefits occur with the addition of ezetimibine to moderately intensive statin therapy, recent acute coronary syndrome, LDL ≥50 mg/dL, or for those intolerant to high intensity statin therapy. Men with triglyceride levels ≥204 mg/dL and a HDL ≤34 mg/dL may benefit from the addition of fenofibrate to statin therapy, but otherwise the combination of fibrates with statin are not recommended. Neither is the combination of statins with niacin as due to an increased risk of cerebrovascular events.

The mechanisms of actions, overall effects of, as well as factors pertinent to patient safety such as precautions, drug interactions, and adverse effects of antihyperglycemic and T2DM comorbid disease management pharmacotherapies are summarized in Table 2.

3.0 Diabetes Management in Traditional Chinese Medicine

3.0.1 Philosophy and Methods of Practice in Traditional Chinese Medicine

Throughout history and across the globe, many countries developed their own methods of medical practices which were eventually acknowledged as their own practice of traditional medicine. TCM has been used to treat the ailments of the peoples of Asia since ancient times and in fact was the only form of medical practice available in China until TMM was introduced by missionaries in the early nineteenth century. TCM employs a number of approaches to achieve a healthy body equilibrium founded on "syndrome" also known as "zheng" or "pattern" differentiation [21]. Zheng differentiation provides the conceptual basis on which TCM is built. Zheng differentiation ultimately uses a combination of "symptoms, syndrome, and disease" to treat several chronic non-communicable diseases [22, 23].

TCM practitioners use four examinations to assess the zheng of a patient [24]. The first examination focuses on the patient's physique, skin complexion, and tongue condition. The second involves listening to the patient's voice to assess respiratory problems such a cough, phlegm as well as evaluating body odors suggestive of ill health. Next, the practitioner will ask the patient how he or she feels overall in terms of their body temperature, perspiration, bowel movements, and thirst etc. Finally, palpations of pulses are used to indicate overall health. The cumulative findings of such examinations suggests a pattern of zheng that establishes a diagnosis and in turn treatment options to resolve underlying problems. Treatment options commonly used in TCM include, but are not limited to the following therapies: herbal medicines, acupuncture, heated cup therapy (cupping), massage therapy (tuina), movement and breathing exercises (qigong), and burnt mogwort therapy (moxibustion).

3.0.2 Xiaoke

TCM has been used to treat DM for more than 2000 years [23, 25]. Initially, practitioners created a word to distinguish a cluster of typical symptoms when diabetes was first observed in ancient China "Xiaoke" 消瘅 [26]. Traditional Xiaoke disease was based on a syndrome or zheng pattern of "three excess and one loss" of the classical presentation of T1DM, excessive thirst, excessive urination, excessive food consumption, and weight loss. The underlying pathological process was believed to be an initial deficiency in yin leading to dryness body heat at times

accompanied with phlegm retention and blood stasis. A prolonged yin deficiency was thought to impair yang leading to qi insufficiency and ultimately leading to a dual deficiency of qi and yin as well as yin and yang. With these beliefs, TCM tenets involve a nourishment of yin with bitter flavors or cold property to enhance qi while clearing of heat from the body promoting fluid production [27-29].

Recently with the escalation of T2DM, there is evidence that the zheng of "three excess and one loss" remains only somewhat applicable to T2DM as half of T2DM patients are asymptomatic initially while 80% of those with symptoms present atypically [30]. It is thought that the excesses and loss syndrome typifies more advanced disease as practitioners are now often diagnosing T2DM prior to the appearance of "three excess and one loss" through physical examination and other biometric indicators especially in suspect individuals with obesity and/or central adiposity [30, 31]. Investigators have recently acknowledged that early and middle stage disease is better represented with a spleen-warm syndrome referred to as "Pi Dan" a direct result of inactivity and an abundance of food consumption. Pi Dan is thought to be caused by an overstimulation of the gastrointestinal tract through too much food consumption leading to excesses in splenic, stomach, liver, gall bladder, and intestinal heats. Similar in TCM pathogenesis evidence of effective management through yin nourishment using herbal preparations with bitter flavor or cold property characteristics [31].

While the philosophy and occupations of TMM and TCM are unalike leading to different methodologies in the diagnosis and treatment of T2DM, there are a few similarities such as the application of nutrition and exercise as treatment modalities. As in TMM, lifestyle interventions in Chinese individuals involving diet and exercise can prevent or delay the progression of prediabetes to T2DM [16]. Without lifestyle intervention, within 20 years approximately 90% of those with prediabetes progress to T2DM and 50% experience at least one cardiovascular event.

3.1 Xiaoke Review of Literature

TCM uses approximately eight hundred different plants and herbs as natural medicines to prevent and treat Xiaokezheng [29]. TCM providers will either give patients a single herb extract, or more often than not a complex formulation of multiple extracts and compounds with the idea of targeting multiple physiological mechanisms within the body to treat T2DM. Unlike TMM where antihyperglycemic medicines typically employ one mechanism of action to lower PBG concentrations, TCM practitioners and researchers proposed that TCM formulations and even single herb preparations often employ a number of mechanisms of action concurrently to do the same [27, 31]. For instance, a review by Wang et al. (2013) proposed that Xiaoke TCM herbal plant extracts used at least one of seven different mechanisms of action many of which act at the same site or on the same physiological pathway as some of the TMM outlined in Figure 1 [27]. As depicted in Figure 2, itemized the mechanisms of actions were as follows: 1) decreased carbohydrate absorption, 2) improved insulin sensitivity, 3) increased peripheral glucose uptake, 4) stimulate insulin secretion, 5) potentiate endogenous incretins, 6) antioxidant effects decreasing cellular apoptosis, and 7) increased glycogenesis or inhibition of hepatic glycogenolysis [27].

Consequently, the aforementioned multiple concurrent mechanisms of actions compounded by inherent difficulties in the quantification of chemical compositions and concentrations of each herb added to a complex formulation that has somewhat hindered the widespread use of TCM as a complementary and alternative medicine (CAM) in TMM. Along these lines, there have also been difficulty determining the therapeutic efficacies of various TCMs due to practitioner variations in preparation techniques and applied doses given to patients based on their evaluations of Xiaoke syndrome differentiation. One final contemplation that could quite possibly be hindering implementations of TCMs into TMM lies specifically within a considerable priority in the provision of healthcare in the western world, patient safety and quality assurance. At present, little is known about the possibility of interactions between or adverse effects of simultaneous combinations of TCM formulations with and commonplace TMMs.

3.1.1 Xiaoke Formulations

In 2007, the China Association of Chinese Medicine published the first set of guidelines adopted by TCM primary care physicians in China concerning the prevention and treatment of DM using TCM. Herbal medicines with bitter flavor and cold property have evidence of effective treatment applications. A synopsis of the most common TCM herbal preparations/concoctions used to treat T2DM is presented below. When provided, proposed mechanisms of actions, overall effects of, as well as factors pertinent to patient safety such as precautions, herb/drug interactions, and adverse effects will be included in the review.

Tianqi

Tianqi is a novel Chinese herbal medicine used to treat T2DM in China [32-34]. Tianqi's herbal quality and decoction preparation is regulated by the Chinese Pharmacopoeia. It is manufactured in capsule form by the Heilongjiang Baoquan Pharmaceutical Company and contains ten herbal medicines.

Ingredients:
Astragali Radix
Coptidis Rhizoma *berberine*
Trichosanthis Radix
Ligustri Lucidi Fructus
Dendrobii Caulis
Ginseng Radix
Lycii Cortex
Ecliptae Herba
Galla Chinensis
Corni Fructus

Proposed MOA of the concoction: not specified

Overall effects:

- overall reduction in risk for diabetes of 32.1% [32].
- *Reduced HbA_{1C} by 1.15%±1.58% [33]*
- *Reduced pre- and 2-hour post prandial blood glucose [33]*

In a multicenter randomized controlled trial by Lian et al (2014), individuals with impaired glucose tolerance were given five capsules thrice daily before meals of either a placebo or Tianqi (1.6g capsules) for twelve months. The contents of the marker compounds in the Tianqi capsules used in this study were as follows: magnoflorine (0.04±0.01 mg/g), berberine (2.14±0.07 mg/g), gallic acid (21.39±0.12 mg/g), astragaloside IV (0.07±0.01 mg/g), palmitic acid (3.55±0.08 mg/g), ginsenoside Rc (0.31±0.01 mg/g), ginsenoside Rd (0.60±0.02), and ginsenoside Re (0.25±0.01). At the end of the study there were no statistical differences in body weight or body mass index changes between the two groups. No serious adverse events were reported, and the common events were related gastrointestinal matters (i.e., nausea, flatulence, constipation, diarrhea). Significantly more subjects developed T2DM in the control group (29.32%) than the Tianqi group (29.32% vs. 18.18%; p=0.01) which reflected an overall reduction in the risk of T2DM development by 32.1% [32]. HbA_{1C} and plasma insulin were not assessed.

An observational study by Zhao et al. (2003) reported a reduction in HbA_{1C} by 1.15%±1.58% as well as pre- and 2-hour post prandial blood glucose levels in 300 individuals with T2DM following 8 weeks of Tianqi ingestion.

Patient Safety:

- **Proposed "similarity in efficacy":**
  - α-glucosidase inhibitor (acarbose)
  - metformin
- **Adverse effects:**
  - gastrointestinal
  - (<1%) rash, weakness, weight loss, polyuria, tinnitus, CBC abnormalities
- **Interactions**: unknown
- **Precautions:** unknown

Kaiyu Qingre Fang (aka Kaiyu Qingre-Jiangzhao or Kaiyuqingre)

Kaiyu Qingre Fang is used to treat diabetes by nourishing yin with bitter flavor and cold to enhance qi while clearing heat form the body [30, 31, 35, 36].

Ingredients:
Scutellariae [35]
Rhizoma Coptidis *berberine [35]*
Chinese Rhubarb [31, 35]
Momordica Charantia [31]
Anemarrhena [31]
"and so on" [31]

Proposed MOA of the concoction:

- improve late phase beta cell secretion of insulin [36]
- contribute to insulin resistance [36]
- reduce fatty acid synthase activity by modifying overexpression of sterol regulatory element binding protein-1c to modulate glucose and lipids [37, 38]

Overall Effects:

- decreased HbA_{1C} by 1.32% [35]
- decreased HbA_{1C} by 1.67% [22, 39]
- "similar to metformin for decreasing glucose "but safer" [22, 39]

In a multi-centered RCT including both TCM and western medicine hospitals in Beijing (n=127) by Lian et al (2008) a control group received metformin and the treatment group received Kaiyu Qingre-Jiangzhuo (KQJ) for 12 weeks. Significant reductions in FBG, P2BG at 4-, 8-, 12-12 weeks as well as HbAlc of 12-weeks were observed in both groups from baseline values (p<0.05). There were not statistically significant differences between the two groups and no adverse effects were reported in the KQJ group.

Patient Safety:

- **Proposed "similarity in efficacy":**
  - similar to metformin "but safer" [22, 39]
- **Adverse effects:** none reported
- **Interactions**: unknown
- **Precautions:** unknown

Tang-Min-Ling-Wan (TM81)

This is another concoction used to treat T2DM by feeding yin with cold property and bitter flavor [31, 40].

Ingredients: **Rhizoma Coptidis** berberine shall not be <6.0mg/g [40]
Chinese Rhubarb [40]
Radices Trichosanthis [40]
Radix Paeoniae Alba paeoniflorin shall not be <3.0 mg/g [40]
Radix Scutellariae [40]
Pericarpium Cirtri Reticulatae [40]
Rhizoma Rhei [40]
"and other Chinese herbs" [40]
Major compounds: berberine, albiflorin, paeoniflorin, naringin, hesperidin, baicalin

Proposed MOA of the concoction:

- triggers insulin secretion in a high glucose environment [40]
- similar to rosiglitazones ability to improve insulin secretions by islet cells by significantly increasing PPARα [41]
- reversion of insulin resistance

Effects:

- decreased HbA_{1C} BY 1.18% [40]
- lowers blood glucose levels (HbA_{1C}, FPG, 2hPG)
- reduces WC and BMI and obesity
- increases β-cell functioning

In a multicenter randomized controlled trial, Tong et al (2013) compared the effects a twelve-week regimen of thrice daily oral ingestion of 6g TM81 to a placebo group in individuals with early stage T2DM in China [40]. Authors note that the content of berberine in Rhizoma Coptidis was not less than 6.0mg/g and paeoniflorin in Radix Paeibuae Alba less than 3.0 mg/g in the final product. At the end of the study the mean HbA_{1C} decreased by 1.02% and 0.47% in the treatment and control group respectively (p<0.001). FPG decreased by 0.8 ±0.1mM in the TM81 group and increased 0.2±0.2mM increase in the control group. HbA_{1C} decreased 1.0±0.7% in the TM81 group versus 0.2±1.0% in the control group (p<0.001) with. Significant differences were found in terms of 2hPPG, body weight, BMI, T2DM symptoms, waist circumference, insulin resistance (HOMA-IR), β-cell functioning (HOMA-β), triglyceride, total cholesterol, HDL, and LDL favoring improved values in the TM81 versus control group. There were no significant differences in the adverse reactions reported between the two groups.

Patient Safety:

- **Proposed "similarity in efficacy":** none reported
- **Adverse effects:** no significant differences between TM81 and control group
- **Interactions**: unknown
- **Precautions:** unknown

Gegen Qinlian Tang (aka Gegen Qin Lian)

Gegen Qinlian Tang is another common TCM preparation used to treat diabetic individuals with damp heat syndrome of the spleen through yin nourishment with bitter flavor and cold to enhance qi while clearing heat form the body [31, 42, 43].

Ingredients:

- **Radix Puerariae** (Ge Gen)	24g, 72g, 120g [43]	1.0g, 24g, 72g, 120g[44]
- **Radix Scutellariae** (Huang Qin)	9g, 27g, 45g [43]	0.4g, 9g, 27g, 45g [44]
- **Rhizoma Coptidis** (Huang Lian)	9g, 27g, 45g [43]	0.4g, 9g, 27g, 45g [44]
- **Radix Glycyrrhizae** (Zhi Gan Cao)	6g, 18g, 30g [43]	
- **Rhizoma Zingiberis** (Gan Jiang)	1.5g, 4.5g, 7.5g [43]	
- **Honey-fried Licorice Root** (Gan Cao)	0.3g, 6g, 18g, 30g [44]	

- Fructus Ziziphi Jujubae (Chao Zao Ren) was added for insomnia [43]
- Jiu Da Huang (Radix et Rhizoma Rhei) was added for constipation [43]
- Spika Prunellae (Xia Ku Cao) was added for liver-yang hyperactivity [43]
- Rumulus Uncariaecum Uncis (Gou Teng) was added for liver-yang hyperactivity [43]
- Hong Qu (Semen Orysae cum Monasco) was added for high blood lipid [43]
- Wei Ling Xian (Radix Clematidis) was added for high uric acid [43]

Proposed MOA:

- reduces glucose metabolism disorders [31]
- reduces insulin resistance [31]
- increases tissues sensitivity to insulin [31]
- improves physiological antioxidant functions [31]
- protects pancreatic function [31]
- induces structural changes in gut microbiota (i.e., increases beneficial bacteria *Faecalibacterium spp.*) [44]

Effects:

- reduced glucose by 91% [45, 46]
- *12 weeks (high dose reduced $HbA1_C$ by 1.79±0.11[43]*
- *12 weeks high dose reduced: [44]*
  - *FPG 1.46±0.23*
  - *HbA_{1C} 0.88±0.14*
  - *HOMAβ*

Tong et al. (2011) examined the effects of two daily oral doses of low, medium, and high doses of Gegen Qin Lian taken on an empty stomach once in the morning and once in the evening for a total of 12 weeks. Pre- and post-FPG, postprandial blood glucose, and HbA_{1C} were measured in the 54 participants. The overall effective rate of blood glucose control of high dosage, medium dosage and low dosage group were 80%, 47%, 30% respectively, and there were significant differences between high dosage group and low dosage group. The decrease of FBG, PBG and HbA_{1C} of high dosage showed significant differences from low dosage too. No placebo/control group. Hepatic and renal function remained unchanged from pre to post intervention. Reported adverse effects were stomachache with postprandial versus preprandial high dose administration and constipation with medium dose.

Xu et al. (2015) In a randomized, double-blinded, placebo controlled clinical trial, Xu et al (2015) examined the 1) efficacy and safety of GQD in the treatment of T2DM, and 2) the structural alterations of gut microbiota in response to GQD treatment. GDP was administered in twice-daily oral, pre-prandial doses. GDQ treatment provided dose dependent and clinically meaningful reductions in FPG, HbA_{1C}, HOMAβ, as well as alterations in gastrointestinal microbial composition. Adverse events/effects were not reported anywhere within the article.

Patient Safety:

- **Proposed "similarity in efficacy":**
  - Sulfonylurea [47, 48]
  - Buiguanides [47, 48]
- **Adverse effects:**
  - stomachache with postprandial (versus pre-prandial) high dose (n=1)[43]
  - constipation medium dose (n=1)[43]
- **Interactions**: unknown
- **Precautions:** unknown

3.1.2 Xiaoke Common Single Ingredients

The previous section reviewed the four most common concoctions used in TCM to treat Xiaoke. Though much of the TCM research has focused on preparations involving multiple ingredients, there is some evidence of single ingredient considerations. Of the four most common TCM preparations identified in the section above, there were several single ingredient commonalities. Specifically, rhizoma coptidis was found in all four formulations and scutellariae was found in three. What follows are in depth reviews of the literature for these two herbs.

Rhizoma Coptidis (Huang Lian)

The primary active ingredient in rhizoma coptidis is berberine [49]. Berberine is a natural plant alkaloid isolated from the Chinese her coptis chiesnensis (huanglain).

Main Ingredient: berberine *(an isoquinoline alkaloid)*

Proposed Mechanisms of Action:

- reduces glucose metabolism disorders
- reduces insulin resistance
- increases tissue sensitivity to insulin
- improves physiological antioxidant functioning
- protects pancreatic function
- increases insulin receptor expression *(in vitro and in animal models)*
- significantly improves insulin signaling
- "insulin sensitizer" in peripheral tissues via protein kinase C-dependent insulin receptor upregulation

Effects:

- reduced glucose by 0.9% [50]
- 90% effective in reversing DM with few side effects [51]
- Same effects as metformin and rosiglitazone on reducing glucose and HbA_{1C}
- More effective at lower lipids than (above)
- Can be used with hepatic insufficiency [52, 53]
- *A randomized double-blind, placebo controlled and multiple center trial by Gu et al. (2010) found significant improvements in fasting and 2-h OGTT plasma glucose and in HbA_{1C}, serum total cholesterol, triglycerides and LDL-c concentrations after a 12 week berberine treatment compared to the control (placebo) group. Berberine, a constituent of Coptidis Rhizoma, was reported to improve glycemic parameters, including glycosylated hemoglobin (HbA_{1C}) and FPG (9–11 of Lian 2014).*

Other effects:

- antimicrobial effects against staphylococcus aureus, methicillin resistant staph aureus, and candida [54, 55]
- antiprotozoal effects again entamoeba histolytica, giardia lamblia, trichomonas vaginalis [54, 55]
- enhances antimalarial effects of drugs in chloroquine resistance strains [54, 55]
- antidiarrheal activity [55]

Patient Safety:

- **Proposed "similarity in efficacy":**
  - metformin, rosiglitazone with greater effects of reducing lipids [31]
  - "similar in efficacy to sulfonylureas and biguanides" [47, 48]
- **AE:** none reported, "safe" for patients [52]
- **Interactions**: none reported
- **Precautions:** none reported
- **Other Proposed Uses of Huang Lian in TCM**
  - Gastrointestinal concerns: Dysentery, vomiting, epigastric "stuffiness" (liver/jaundice, eczema, gall bladder, bladder)
  - Cardiovascular, stomach, and liver concerns
  - Insomnia
  - Mouth or tongue sores
  - Abscesses, furuncles, carbuncles

Radix Scutellariae (Huang Qin), Scutellaria Baicalensis Georgi

Main Ingredient: wogonin (5,7-dihydroxy-8-methoxyflavon)

Proposed Mechanisms of Action:

- enhances peroxisome proliferator-associated receptor (PPAR) α isoforms and adiponectin expression through AMP-activated protein kinase (AMPK) activation
- suppress osteopontin (OPN) expression [56]
- improves cardiac function in diabetic cardiomyopathy

Effects:

- improve insulin sensitivity
- reduces fasting blood glucose
- ameliorates glucose tolerance
- Improves cardiac function in diabetic cardiomyopathy

Other effects:

- Anti-cancer effects anti-inflammatory, anti-apoptosis, and anti-allergic properties [57-61]
  - scavenges reactive oxygen species
  - attenuates nuclear factor kappa-light-chain-enhancer of activated B cell activity
  - inhibit several genes important for regulation of the cell cycle responsible for cytostatic effects
  - suppresses cyclooxygenase (COX-2) gene expression
  - prevents viral infections
  - selectively induces apoptosis in tumor cells with minimal or no toxicity in normal cells

Patient Safety:

- **Proposed "similarity in efficacy":** none reported
- **AE:** none reported
- **Interactions**: none reported
- **Precautions:** none reported
- **Other Proposed Uses of Huang Qin in TCM**
  - Relieves heat from high fever, abscesses, sores, sore throat
  - Stops bleeding (blood cooling and bleeding stopping herb) in hematemesis, hemoptysis, melena, hematuria, metrorrhagia, epistaxis
  - Abortion prophylaxis

Table 5 catalogs claims found within the literature relating to the proposed mechanisms of action, precautions, and adverse effects of five other herbs found in the most common TCM herbal preparations identified in section 3.1.1.

4.0 Future Directions

The popularity of TCM use has escalated and herbal preparations are now widely available and used throughout USA, Europe, and Australia. In 2010, the US was the biggest importer of TCM articles from China having spent over 7.5 billion dollars on product. According to the CDC, approximately 38% of US adults use some form of Complementary and Alternative Medicine (CAM) with the most utilized therapy being non-vitamin, non-mineral natural products [62]. In the US, TCM herbal preparations or supplements are considered a form of CAM or even at times a nutritional supplement, but are for the most part unregulated by the Food and Drug Administration (FDA). Such ambiguity and paucity in the regulation of TCMs evokes ruminations of the hazards and ill effects of ingesting unknown and unregulated substances [63].

Beyond this obvious avenue of thought, there is also a lack of quality research to establish the possible clinical efficacies and safety profiles of TCMs. Clinical trials comparing the effectiveness of TMMs to TCMs in diabetes management are thus justified and warranted. Should these trials of comparative effectiveness find certain TCMs to be inferior or even superior to the TMMs detailed in current T2DM clinical practice guidelines, support for the credibility of TCMs would be attained and may even facilitate the approval of Xiaoke herbal medicines by the FDA.

At present, some research scholars divulge differing opinions about the manner in which TCMs should be implemented in clinical trials of efficacy and even the use of TCM in the modern era in general. Some scholars are certain that TCMs should be quantified, certified and regulated using the rigorous processes that led to the approvals of TMMs for use in the treatment of T2DM in the US, while others trust TCMs should be adopted consistent with the underlying philosophy and methods of practice in TCM as described beforehand. In other words, what

is otherwise understood as lack of regulation or vagueness in the doses and compositions of TCM prescriptions and therapies by some parties has actually initiated the announcements of a number of future research foci. For instance, the World Health Organization recognizes a need to identify underlying mechanism of actions in TCM ingredients and has subsequently endorsed an international agreement to support the safe and effective use of TCM within established health care systems of its member states [64]. In time, this will result in TCM preparations becoming as formally defined as TMM medicines (i.e., quantification, clinical efficacy, dosing, pharmacokinetics, pharmacodynamics, adverse effects, precautions etc.) prior to their use in its member states. Such formal definitions of TCMs may generate a wider acceptance of TCM in medical practices in western civilizations. Conversely, the Chinese government and its research community are continuing efforts to regulate traditional herbal medicines just as they evolved from their underlying philosophical system and subsequently implemented in medical practices to treat diabetes for thousands of years. China's FDA promulgated a 2015 edition of the Chinese Pharmacopoeia that promotes the utilization, production, and supervision of Chinese drugs with intent to ensure drug safety and effectiveness for its public [65].

Irrespective of the approach used to implement TCMs in clinical trials of efficacy, we are of the opinion that the most imperative outcome is effective management of T2DM. Therefore, in addition to ultimately supporting those medicines with established clinical efficacy, we advocate for international research collaborations and overall global capacity building. In doing so, it is entirely possible that in the future, a combination T2DM management strategy from both Chinese and western medical practices may be most effective. In fact, a number of Chinese researchers have already proposed theories describing how TCM and TMM can be implemented together to manage diabetes and its sequelae across the disease spectrum [27, 30, 66].

Much more troublesome than the different operational approaches to TCM employed in clinical trials is the limited knowledge of the potential implications of the concurrent use of TCM and TMM in those who require multiple TMMs to effectively manage a chronic non-communicable disease such as diabetes. Encouraged by concerns of patient safety and the provision of quality healthcare in the US, we suggest that research efforts begin with initial and continued careful evaluations of those who concurrently use TMM, TCM, and other nutritional supplements with particular attention paid to those with T2DM using five or more TMM medications. Programs associated with patient safety such as Patient Safety Organizations (PSO) are uniquely poised to easily complete these types of evaluations and detect any safety related concerns with concurrent uses of TMM and TCM.

With pragmatic approaches to document the comparable efficacies of TCMs as well as the prevalence, incidence, and evaluations of the effects of concurrent uses of TMM and TCM use in T2DM identified, we can now contemplate other matters. Earlier we alluded to a possible attractiveness of TCM use in T2DM due to its affordability especially when compared to the increasing costs of TMM, health care insurance, and other health care related costs. We also mentioned the cultural significance of TCM to individuals of Asian descent who are predisposed to T2DM. The spectacular increase in the number of Asian immigrants to the US in the past few decades highlights an important research opportunity in a targeted population. New York City has one of the highest Asian American populations within the US. Previous research has documented the feasibility of data collection in this population within this context. For example, the New York City Health and Nutrition Examination Survey found that almost half of the NYC Asian Americans had prediabetes or diabetes at a lower relative body weight than other population groups [67]. Thus, research about T2DM in Asian American populations in NYC is feasible. Given their access to a variety of culturally acceptable means of blood glucose control, documentation of their TCM use is an admirable opportunity.

It is well known that upon arrival to the US, immigrants are often healthier that those born in the US with lower body mass indexes, higher fruit and vegetable consumptions, and higher levels of certain physical activities [68-75]. An explanation for these health advantages in first generation immigrants is their maintenance of the cultural beliefs stemming from their country of origin. Another beneficial outcome of research relating to the use of TCM in Asian American populations is documentation of second, third, fourth etc. generation immigrants that have likely become 'westernized'. In other words, subsequent generations of immigrants to the US are likely exposed to the cultural beliefs of their family's original countries of origin however; their belief systems may have been 'Americanized'. Support for this theory comes from evidence of associations of the duration of time spent in the US with overweight and obesity. For example, both Chinese and Filipino immigrants living in NYC for longer durations had higher overweight and obesity risks [76, 77].

The concept of 'Americanization' allows for the speculation of a further value to research documenting TCM use in America. Race and ethnicity are known as risk factors for T2DM. In addition to some Asian Americans, other minorities also have a higher risk of T2DM than Caucasians such as African Americans, Hispanics and Latinos, American Indians, and Pacific Islanders. Nevertheless it remains unknown to what, if any, extent these minorities use TCMs or other economical dietary supplements with hopes of controlling their prediabetes or diabetes [78]. According to National Health and Nutrition Examination Survey data, over half (52%) of those surveyed reported the use of a dietary supplements in the preceding 30 days [79]. With such a large percentage of Americans reporting the use of dietary supplements and the Centers for Disease Control and

Prevention actively working to reverse the epidemic of diabetes in the US, further understanding is warranted.

The principal objective of the current article was to initiate our understanding of TCM by identifying and summarizing existing literature on the most common TCM Xiaoke preparations and disease management strategies from a TMM perspective. TCM researchers and practitioners have made similar efforts to disseminate knowledge concerning their applications of herbal treatments in diabetes so that "the Western people know more about anti-diabetic TCM" [31]. The current article also discussed fundamental differences between the two approaches to medicine in terms of their underlying philosophies, theories, and methods of practice as these differences are often cited as reasons as to why their concurrent practice is problematic. It is our hope that continued discussions such as this will facilitate global partnerships with the same research agendas. Ensuring the safety and efficacy of TCM requires a great deal of research that could be completed in a timely manner through international collaboration. Therefore, it is important for researchers across the globe to first understand each other in order to work together effectively toward a common goal while ensuring patient safety.

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Table 1.
Criteria for the Diagnosis and Prediabetes and Diabetes

Variable	Prediabetes	Diabetes
Hemoglobin A_{1C} (%)	5.7-6.4	≥6.5
Fasting plasma glucose level		
mmol/L	5.6-6.9	7.0
mg/dL	100-125	≥6.5
Oral glucose tolerance test results*		
mmol/L	7.8-11.0	11.1
mg/dL	140-199	≥200†
Random plasma glucose level		
mmol/L	-	11.1
mg/dL	-	≥200‡

* 2h plasma glucose level after a 75g oral glucose tolerance test
† In the absence of unequivocal hyperglycemia, results should be confirmed by repeated testing.
‡ Diagnostic only in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Note. Reprinted from "Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes." by J. J. Chamberlain, A. S. Rhinehart, C. F. Shaefer, and A. Neuman, 2016, Annals of Internal Medicine, 164, p. 543. Copyright © 2016 American College of Physicians.

Table 2.

Pharmacodynamics and important patient safety related factors of common T2DM treatments.

	Mechanism of Action	Precautions	Adverse Reactions
Metformin	- Inhibits hepatic gluconeogenesis - Decreases intestinal absorption of glucose - Enhances peripheral muscle glucose uptake and utilization	Precautions: - eGFR<60 - metabolic acidosis - lactic acidosis - dehydration - sepsis - surgery - DKA - Hepatic impairment Cautions: - CHF - Elderly - Alcohol abuse - Hypoglycemia risk - eGFR<60 - Discontinue prior to iodinated contrast imaging	- GI (diarrhea, nausea, vomit, flatulence, indigestion, abdominal discomfort, anorexia, metallic taste) - Rash - Headache - Asthenia - Ovulation induction - Lactic acidosis - Megaloblastic anemia
Sulfonylureas *Glyburide* *Glipidize* *Glimepride* *Acetohexamide* *Chlorpropramide* *Nateglinide* *rosiglitazone* *Tolazamide* *Toblutamide* *Torsemide*	- Insulin secretagogue - Stimulates pancreatic islet beta insulin release - Increase insulin receptors in peripheral tissues	Precautions: - Hypersensitivity (class, sulfonamides) - DKA - T1DM Cautions: - Elderly - Hearing impairment - Hepatic impairment - Acute MI - Arrhythmia - renal impairment (hypoglycemia) - malnutrition - G6PDs	- Diarrhea - Nausea - Hypoglycemia - Dizziness - Nervousness - Tremor - Rash - Headache - Drowsy - Photosensitivity - Hypoglycemia - Leukopenia - Thrombocytopenia - Hemolytic anemia - Rash - Purpura - Pruritus - Antithyroid activity - Diffuse pulmonary reactions - Mild diuresis - Fluid retention - Nausea, vomit, cholestasis - Agranulocytosis - Hepatitis - Hepatic failure - Hyponatremia - Disulfiram-like effect - SIADH - Aplastic anemia

Thiazolidinediones *Pioglitazone* *Rosiglitazone*	- Reduces insulin resistance in peripheral tissue via PPAR gamma system - Enhances insulin action in muscle, liver, fat tissue (insulin sensitizer) - Lipid lowering, mild antihypertensive, decreases hepatic glucose effects	Precautions: - Pediatric - T1DM - DKA - Active bladder cancer - CHF (symptomatic or NYHA Class III-IV) Cautions: - CHF (risk of, NYHA Class I-II) - Edema - hepatic impairment - PMH bladder cancer - female	- URTI - Headache - Myalgia - Edema - Weight gain anemia - Ovulation induction - CHF - Hepatotoxicity - DM macular edema - Bladder cancer (long term use) - Fractures (female)
Dipeptidyl Peptidase 4 (DPP-4) Inhibitors *Sitagliptin* *Saxagliptin* *Linagliptin* *alogliptin*	- Inhibits dipeptidyl peptidase-4 - Slows incretin metabolism - Increases insulin synthesis/release - Decreases glucagon levels - Prolongs the action of incretin hormones (GLP-1, GIP)	Precautions: - Hypersensitivity - T1DM - DKA Cautions: - Pancreatitis - CrCl <50	- URTI - Headache - Diarrhea - Abdominal pain - Arthralgia - Hypersensitivity - Anaphylactoid reaction - Stevens-Johnson syndrome - Pancreatitis - Acute renal failure - Severe arthralgia
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors *Canagliflozin* *Dapagliflozin* *empagliflozin*	- Inhibits sodium-glucose cotransporter 2 (SGLT2) - Reduces glucose reabsorption - Lowers renal glucose threshold (increases urinary glucose excretion)	Precautions: - DKA - Volume depletion - eGFR<45 Caution: - eGFR 45-59 - concurrent nephrotoxic use - risk ketoacidosis - pancreatic insulin deficiency - prolonged fasting - alcohol abuse - hyperlipidemia - PMH genital mycotic infection, UTI - Uncircumcised males	- UTI - URTI - Genital mycotic infections - Increased urination - Dyslipidemia - Increased hematocrit - Arthralgia - Nausea - Increased creatinine - Orthostatic hypotension - Renal impairment - Ketoacidosis - Serious UTI
Glucagon-Like Piptide-1 Agonists (GLP-1) *Exenatide* *Liraglutide* *Albiglutide* *Dulaglutide*	- Activates GLP-1 receptors - Stimulates glucose dependent insulin release - Reduces glucagon secretion - Slows gastric emptying	Precautions: - Hypersentivity - IM or IV administration - T1DM - DKA - PMH pancreatitis - CrCl <30 Cautions: - Risk pancreatitis - Severe gastroparesis - Severe GI disease - Concurrent nephrotoxic agent use - Renal transplant - CrCl <50	- Nausea - Vomit - Diarrhea - Hypoglycemia - Constipation - Headache - Dyspepsia - Hypersensitivity - Anaphylaxis - Nephrotoxicity - Pancreatitis

Aspirin	- nonselective and irreversibly inhibits cyclooxygenase - reduces prostaglandin and thromboxane A2 synthesis - resultant anti-inflammatory, anti-pyretic effects, reduction of platelet aggregation	Precautions: - Hypersensitivity - ASA or NSAID induced asthma, urticarial - GI bleed - Disordered coagulation - G6PD deficiency - Uncontrolled hypertension - Influenza, varicella, or febrile viral infection in <20y/o Cautions: - ≥60y/o - Thrombocytopenia - Surgery - Trauma - Intracranial lesion - Increased intracranial pressure - Chronic alcohol use - Peptic ulcer disease - PMH GI bleed - GERD - Gout - Renal impairment - Hepatic impairment - Sodium restriction	- Dyspepsia - Nausea - Vomit - Abdominal pain - Tinnitus - Dizziness - Hyperuricemia - Bleeding - Ecchymosis - Constipation - Diarrhea - Anaphylaxis - Angioedema - Bronchospasm - Bleeding - GI perforation/ulcer - DIC - Pancytopenia - Aplastic anemia - Agranulocytosis - Nephrotoxicity - Hepatotoxicity - Reye syndrome
ACE-I	- Inhibits angiotensin converting enzyme - Prevents conversion of angiotensin I into angiotensin II	Precautions: - Hypersensitivity - Angioedema (ACE-I, hereditary, idiopathic) - Pregnancy Cautions: - Renal artery stenosis - Renal impairment - Severe CHF - African American - Volume depletion - Hyponatremia - Hypotension - Aortic stenosis - Hypertrophic cardiomyopathy - CAD - Cerebrovascular disease - Collagen vascular disease - Dialysis with high flux membranes	- Dizziness - Hypotension - Headache - Fatigue - Cough - Hyperkalemia - Elevated BUN, Cr - Photosensitivity - Hyperuricemia - Anaphylactoid reaction - Angioedema (head, neck, interstitial) - Stevens-Johnson syndrome - Toxic epidermal necrolysis - Erythema multiforme - Severe hypotension - Hyperkalemia - Renal impairment/failure - Hepatotoxicity - Neutropenia - Agranulocytosis - Pancreatitis - teratogenic

Statin	- 3-hydroxy-3-methylglutaryl-conenzyme A (HMG-COA) reductase inhibition	Precautions: - Hypersensitivity - Pregnancy - Breastfeeding - Myopathy - Unexplained LFT elevations - Active hepatic disease Cautions: - Alcohol abuse - ≥65 y/o - Female - Renal impairment - PMH hepatic disease - Diabetes mellitus - hypothyroidism	- Infection - CK elevations - Headache - Arthralgia - Sinusitis - Back pain - Flu syndrome - Pain - Flatulence - Myalgia - UTI - Abdominal pain - Diarrhea - Asthenia - Elevated ALT, AST - Decrease CoQ10 - Hyperglycemia - Cognitive impairment - Myopathy - Rhabdomyolysis - Acute renal failure - Hepatotoxicity - Pancreatitis - Hypersensitivity - Anaphylaxis - Angioedema - Lupus erythematosus - Polymyalgia rheumatica - Dermatomyositis - Vasculitis - Thrombocytopenia - Leukopenia - Hemolytic anemia - Photosensitivity - Toxic epidermal necrolysis - Erythema multiforme - Stevens-Johnson syndrome

Table 3.
Recommendations for Statin and Combination Treatment in Persons with Diabetes

Risk Factors, by Age	Recommended Statin Intensity*
<40y	
None	None
ASCVD risk factors†	Moderate or high (C rating)
ASCVD	High
40-75y	
None	Moderate (A rating)
ASCVD risk factors	High (B rating)
ASCVD	High
ACS, LDL cholesterol level >1.3 mmol/L (>50 mg/dL), and inability to tolerate high-dose statin therapy	Moderate plus ezetimibe (A rating)
<75y	
None	Moderate (B rating)
ASCVD risk factors	Moderate or high (B rating)
ASCVD	High
ASCVD, LDL cholesterol level >1.3 mmol/L (>50 mg/dL), and inability to tolerate high-dose statin therapy	Moderate plus ezetimibe (A rating)

Note. ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; LDL = low-density lipoprotein.
* In addition to lifestyle therapy.
† LDL cholesterol level ≥2.6 mmol/L (≥100 mg/dL), high blood pressure, smoking, overweight or obesity, and family history of premature ASCVD.

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Table 4.
High- and Moderate-Intensity Statin Therapy*

High-intensity
- Atorvastatin, 40-80 mg
- Rosuvastatin, 20-40 mg

Moderate-intensity
- Atorvastatin, 10-20 mg
- Rosuvastatin, 5-10 mg
- Simvastatin, 20-40 mg
- Pravastatin, 40-80 mg
- Lovastatin, 40 mg
- Fluvastatin XL, 80 mg
- Pitastatin, 2-4 mg

* Once-daily dosing.
† Decreases low-density lipoprotein cholesterol level by ≥1.3 mmol/L (≥50 mg/dL).
‡ Decreases low-density lipoprotein cholesterol lebel by 30% to <50%.

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Table 5.

Proposed pharmacodynamics and important patient safety related factors of other single herbs used to treat T2DM in TCM.

	Mechanism of Action	Precautions	Adverse Reactions
Trichosanthis Radix ***Common name: Trichosanthes root; Chinese Cucumber (Tianhuafen)***	Not reported.	Interacts with the following antihyperglycemic medications: - glimepiride - glyburide - insulin - pioglitazone - rosiglitazone - chlorpropamide - glipizide - tolbutamide	- This herb should be used with caution during pregnancy. - Chinese cucumber ROOT contains a chemical that might cause abortions during the first trimester of pregnancy. - allergic reactions - seizures - fever - fluid retention (lungs, brain) - bleeding (brain) - heart damage and death - might lower blood sugar levels
Astragali Radix **Common name: Astragalus root (Huang qi)**	Not reported.	- Decreases the effectiveness of Cyclophosphamide - Decreases lithium excretion - Decreases effectiveness of immunosupressants (*azathioprine, basiliximab, cyclosporine, daclizumab, muromonab-CD3, mycophenolate, sirolimus, prednisone, corticosteroids)*	- Astragalus might make the immune system more active resulting in the worsening of the symptoms of auto-immune diseases.
Ligustri Lucidi Fructus ***Common name: Glossy privet fruit (Nuzhenzi)***	Not reported.	Interaction: lithium	-Glossy privet may cause an allergic reaction in people who are sensitive to the Oleaceae family of plants
Ginseng Radix	It is thought that ginseng contains a variety of chemicals called ginsenosides that are responsible for its effects. In herbal therapy, Ginseng is often used as an adaptogenic herb, which means that it can regulate a hypo or hyper functioning system.	Interaction: - warfarin - alcohol - MAOIs - Furosemide - Insulin - anticoagulants - antiplatelet drugs - stimulants - drugs metabolized in the liver	- thrombus formation - headache - tremor - mania - increased alcohol clearance -may worsen autoimmune diseases -interferes with blood clotting -might lower BP -linked with insomnia
Corni Fructus ***Common name: Dogwood fruit (Shanzhuyu)***	Not reported	None reported.	-Deficiency of the liver and kidneys manifested as dizziness, blurred vision, soreness in the lower back, weakness of the legs, seminal emissions and impotence -Spontaneous sweating due to weakness of the body.

Figure 1. ***Antihyperglycemic therapy for type 2 diabetes mellitus: general recommendations.***

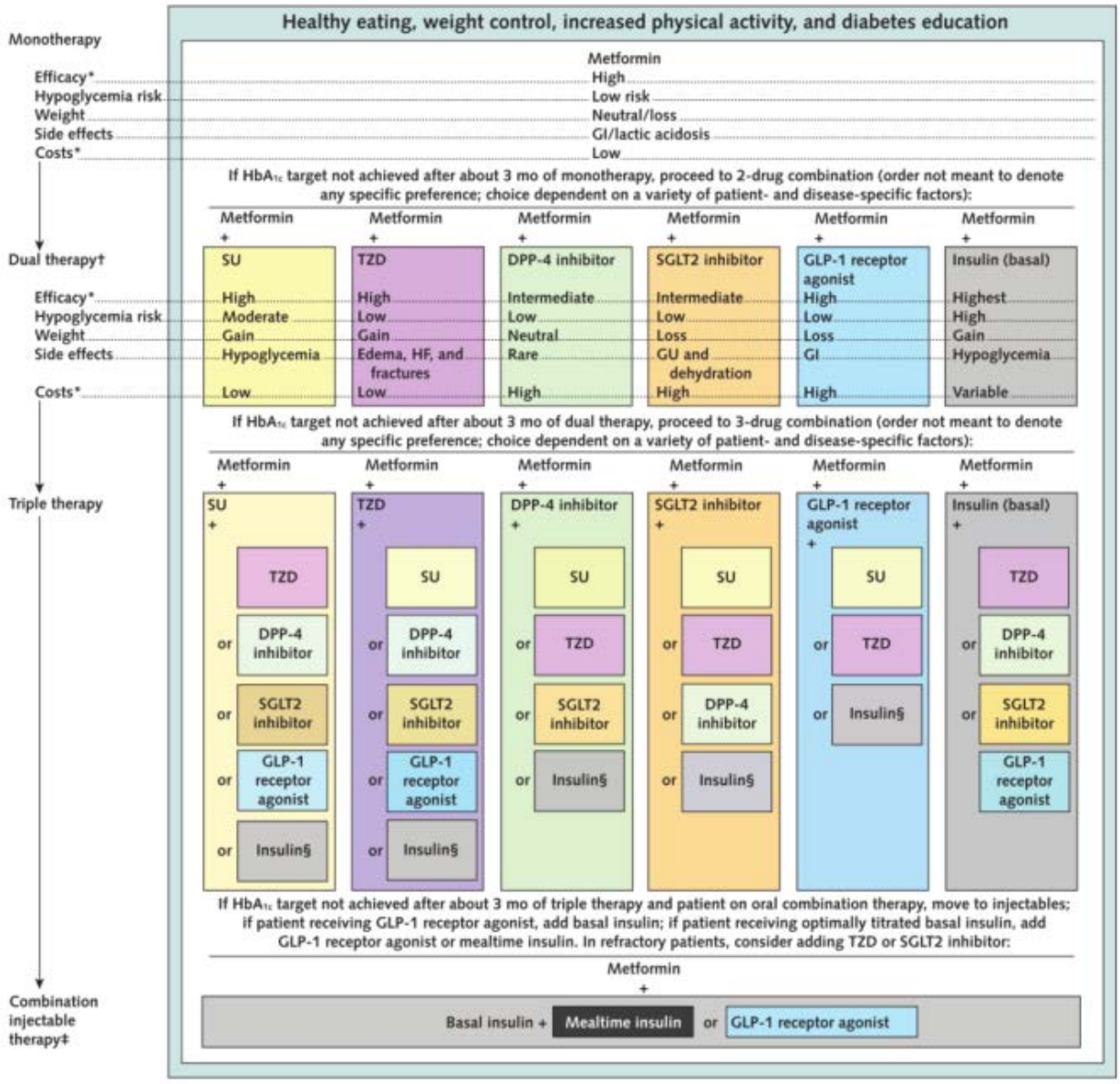

Figure 1. The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is nor meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patient with type 2 diabetes mellitus are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances).

* See Inzucchi et al. (2015) [80] for description of efficacy categorization.

† Consider starting at this stage when the HbA_{1C} level is 9% or greater.

‡ Consider starting at this stage when blood glucose levels are 16.7 to 19.4 mmol/L (300 to 350 mg/dL) or greater and/or HbA_{1C} levels are 10% to 12%, especially if symptomatic or catabolic features are present (in which case basal insulin plus mealtime insulin is the preferred initial regimen).

§ Usually a basal insulin (neutral protamine Hagedorn, glargine, detemir, or degludec).

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Figure 2. A summary of the proposed mechanisms of antidiabetic effects of commonly utilized Traditional Chinese (TCM) and Indian Medicine (TIM) formulations and single herb ingredients alongside the established mechanisms of Traditional Modern Medicines (TMM).

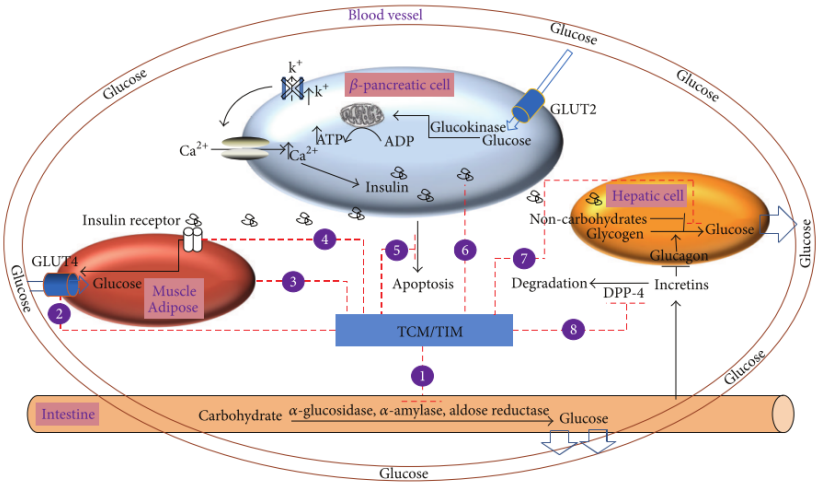

Figure 2. The numbered mechanisms of actions corresponding to those depicted above:

Mechanism of Action	TCM/TIM	TMM
(1) Reduced carbohydrate absorption, such as inhibition of α-glucosidase, α-amylase, and aldose reductase	KQF [N †] GQT [N † ‡]	Metformin Acarbose
(2) increased glucose uptake in muscle and adipose tissues	RC [N † ‡]	Metformin Sulfonylureas Thiazolidinediones
(3) activation of PPAR	TM81 [N §] GQT [N † ‡] RS [N §]	Thiazolidinediones
(4) increased insulin sensitivity/ upregulation of receptor expression	TM81 [N §] RC [N † ‡] RS [N §]	Metformin
(5) exertion of antioxidant effects and decreasing β-cell apoptosis	GQT [N † ‡] RC [N † ‡]	
(6) stimulation of β-cell insulin secretion	TM81 [N §] KQF [Y †] GQT [N † ‡]	Metformin Sulfonylureas DPP-4 inhibitor GLP-1 receptor agonist
(7) inhibition of hepatic gluconeogenesis/ glycogenolysis		Thiazolidinediones DPP-4 inhibitor
(8) prevention of endogenous incretins from degradation/suppression of glucagon		DPP-4 inhibitor GLP-1 receptor agonist

KQF: Kaiyu Qingre Fang (≥6 ingredients); TM81: Tang-Min-Ling-Wan (≥8 ingredients); GQT: Gegen Qinlian Tang (≥6-12 ingredients); RC: Rhizoma Coptidis (single herb); RS: Radix Scutellariae (single herb); Tianqi (TCM, formulation reviewed but not listed in table above, 10 ingredients) [N † ¥ U]

[N] No existing evidence of clinical research comparing efficacies
[Y] Existing evidence of clinical research comparing efficacies
Proposed "similarity in efficacy" :
[§] not known or specified [†] metformin/biguanides [¥] α-glucosidase inhibitor [‡] sulfonylureas
[U] mechanism unknown or else not specified

Adapted from "Treating type 2 diabetes mellitus with traditional Chinese and Indian medicinal herbs." by A. Wang, J. Wang, and P. Chan, 2013, Evidence-Based Complementary and Alternative Medicine, 2013, 343594. Copyright © 2013 Zhijun Wang et al.