Ancient Records and Modern Research on the Mechanisms of Chinese Herbal Medicines in the Treatment of Diabetes Mellitus

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Over the past decades, Chinese herbal medicines (CHM) have been extensively and intensively studied from both clinical and experimental perspectives and CHM have been proved to be effective in the treatment of diabetes mellitus (DM). This study, by searching ancient records and modern research papers, reviewed CHM in terms of their clinical application and principal mechanisms in the treatment of DM. We summarized the use of CHM mentioned in 54 famous ancient materia medica monographs and searched papers on the hypoglycemic effect of several representative CHM. Main mechanisms and limitations of CHM and further research direction for DM were discussed. On the basis of the study, we were led to conclude that TCM, as a main form of complementary and alternative medicine (CAM), was well recorded in ancient literatures and has less adverse effects as shown by modern studies. The mechanisms of CHM treatment of DM are complex, multilink, and multitarget, so we should find main hypoglycemic mechanism through doing research on CHM monomer active constituents. Many CHM monomer constituents possess noteworthy hypoglycemic effects. Therefore, developing a novel natural product for DM and its complications is of much significance. It is strongly significant to pay close attention to CHM for treatment of DM and its complications.

1. Introduction

Diabetes mellitus (DM), including type 1 and type 2, has become epidemic worldwide [1–3], and its incidence has been on rise year by year [4]. Previous reports have demonstrated that overweight, especially obesity at younger ages, substantially increases the risk for DM [1, 5–8]. The finding is consistent with the description in the “Medical Classic of the Yellow Emperor,” the earliest monumental work on the traditional Chinese medicine (TCM) dating back to the Warring States Period (about 446 B.C.–221 B.C.). DM increases the risk for micro- and macrovascular complications and premature death and poses tremendous socioeconomic burden [2, 4, 9]. In spite of the introduction of insulin and other hypoglycemic agents, so far, no treatment protocols can achieve a complete cure. Moreover, the side effects of these drugs, which are substantial and inevitable, present another challenge.

Complementary and alternative medicine (CAM) have been extensively used in modern times. TCM, as a main form of CAM, has been proved to be effective for the treatment of DM with relatively less side effects in China and beyond [10, 11]. Some hypoglycemic drugs of plant origin have been approved for clinical use by the regulatory authorities in China, such as Yusanxiao, Yijin, and Kelening, among others [12].

The mechanisms of Chinese herbal medicines (CHM) in the treatment of DM have been extensively and intensively studied from biological, immunological, and phytochemical perspectives and great advances have been made in the past decades. This paper reviewed records or descriptions concerning the use of CHM for treatment of DM in ancient Chinese literatures (before 1920 A.D.) and the modern papers on the mechanisms of CHM treating DM. We also compared the CHM used in ancient and modern times, examined the
Table 1: A similar comparison of the symptoms of “Xiao Ke” and DM.

| General symptoms | Symptoms of “Xiao Ke” in Zhu Bing Yuan Hou Lun 4 | Symptoms of DM in Textbook of Internal Medicine [22] |
|-------------------|--------------------------------------------------|--------------------------------------------------|
| Symptoms          | Polydipsia; dry mouth and lips; polyphagia; hunger; emptiness of the stomach; frequent urination; polyuria; glucosuria; emaciation; adiposity; fatigue of limbs; mental fatigue; feverish dysphoria; itchy skin; hyperhidrosis; dizziness; sweet feeling in the mouth. | Polydipsia; thirst; polyphagia; hunger; polyuria; marasmus; obesity; sweet taste of urine; itchy skin; vulva pruritus; fatigue; lightheadedness. |
| Complications     | Carbuncle and soreness; night blindness; internal oculopathy; lung tuberculosis; edema; precordial pain; pectoral stiffness pain; apoplexy; coma; impotence; foot carbuncle-abscess; unsmooth defecation; diarrhea; anorexia; short breath; waist soreness; dizziness and tinnitus; pachylosis; whitish and turbid urine; muscle atrophy of the lower extremities; oliguria; nightly sweating; coolness of extremities. | Carbuncle and furuncle; diabetic retinopathy; pulmonary tuberculosis; diabetic cardiomyopathy; diabetic ketoacidosis; diabetic impotence; glaucoma; diabetic nephropathy; atherosclerosis; cerebral ischemic stroke; diabetic foot; constipation; diarrhea; myophagism; paralysis; oliguria; hyperhidrosis; hypohidrosis or anhidrosis; diabetic gastroparesis. |

4The “Zhu Bing Yuan Hou Lun”: a book describing causes and manifestations of diseases by Yuanfang Chao, a famous TCM doctor born about AD 550 and died in 630 A.D. in the Sui Dynasty.

limitations of CHM for treating DM, and discussed the future research trend.

2. Ancient Records on Treatment of DM with TCM

Our search of literatures of TCM (before 1920 A.D. or earlier) failed to find the term “DM.” We found a plenty of records or descriptions about “Xiao Ke,” which, in terms of epidemiology, symptoms, etiology, pathogenesis, and treatment, mimicked those of DM. And it is generally accepted that “Xiao Ke” mentioned in ancient Chinese literature is similar to DM of modern medicine [13]. On basis of this assumption, in this paper, we used DM interchangeably with “Xiao Ke” for the convenience of discussion though they are not strictly equivalents in a number of ways.

2.1. Terminology, Epidemiology, Symptoms, Etiology, and Pathogenesis of “Xiao Ke”

2.1.1. Name. In TCM, “Xiao Ke” refers to a cluster of clinical symptoms, including polydipsia, polyphagia, polyuria, emaciation, glucosuria, and fatigue. As aforementioned, “Xiao Ke” is a general term for a condition that resembles DM in terms of symptoms. DM classically was divided into three types: upper, middle, and lower “Xiao Ke.” The upper type (Shang Xiao) is characterized by excessive thirst, the middle type (Zhong Xiao) by excessive hunger, and the lower type (Xia Xiao) by excessive urination [13]. By searching “Xiao Ke,” we retrieved a large number of records concerning “Xiao Ke” in ancient TCM literatures.

2.1.2. Epidemiology. The earliest mention of “Xiao Ke” was in the “Medical Classic of the Yellow Emperor.” The book described that the “Xiao Ke” was mostly found in wealthy, obese individuals who liked food rich in oil or fat and in influential officials who were on pills or “Dan,” as it was termed in the book, a mineral-based synthetic drug, which ancient people believe to be able to make them achieve longevity.

2.1.3. Symptoms. The symptoms can be categorized into two groups: general symptoms and complications. The general symptoms include polydipsia, polyphagia, polyuria, glucosuria, emaciation, dry mouth, hunger, emptiness of the stomach, and frequent urination. And complications include diabetic foot, diabetic retinopathy, lung tuberculosis, diabetic impotence, and diabetic nephropathy. Obviously, those symptoms and complications are extremely similar to DM, as shown in Table 1.

2.1.4. Etiology and Pathogenesis. According to the theory of TCM, the symptoms are essentially caused by “Yin Xu” (Yin deficiency) and “Zao Re” (dryness heat). In TCM there is a belief that Yin deficiency is the “Ben” (origin or root cause) and dryness heat is the “Biao” (symptoms or external manifestations). The Ben or root causes involve the invasion of exogenous pathogens, innate deficiency, intemperance in eating, abnormal emotional states (anger, anxiety, depression, distress, panic, and fear), excessive physical strains (mental or physical exertion and sexual intercourse), or propensity for abusing Dan medicines [11]. Yin and Yang are two opposing aspects of things. For instance, cold, moist, night, structure, and downward mobility belong to Yin while heat, dryness, day, function, and upward mobility belong to Yang [14].

2.2. Treatment. We searched for the term “Xiao Ke” in more than 1,000 TCM ebooks included in Encyclopedia of TCM (Compact Disk, ISBN: 7-900377-49-2/R-8), published by Hunan Electronic and Audiovisual Publishing House. The database contained, among others, “Bencao Gangmu (Compendium of Materia Medica)”, Puji fang, and so forth.

2.2.1. CHM. We also searched the database for Chinese crude drugs for treating “Xiao Ke.” The database contained only 54 monographs on Chinese materia medica. Most CHM treated "Xiao Ke" by "Qing Re" (clearing heat) (Figure 1),
“Yang Yin” (nourishing Yin), and “Yi Qi” (replenishing vital energy) (Figure 2). The Latin names of CHM used in the paper were from the website http://www.theplantlist.org/ or http://www.wikipedia.org/.

2.2.2. Foods. Besides, the monographs also mentioned some foods that help treat “Xiao Ke” in Figure 3.

3. Mechanisms by Which CHM Work on DM and Its Complications

We searched the databases of PubMed, Web of Science, MEDLINE, and CNKI and found that less research attention was paid to Chinese herbal compounds while most studies focused on a single herbal medicine.

The mechanisms of CHM in the treatment of DM have been extensively and intensively studied from biological, immunological, and phytochemical perspectives (Tables 2, 3, and 4).

4. Results

We found more than 40 CHM with hypoglycemic effect in ancient works and reviewed the mechanism of CHM lowering blood sugar. We were led to conclude that a number of CHM, including Panax ginseng C. A. Mey., Astragalus membranaceus (Fisch.) Bunge, and Lonicera japonica Thunb., were used in ancient times and also nowadays. In addition, some CHM used for treating DM in ancient works have not been studied for hypoglycemic effect in modern times, such as Lemma minor L., Gardenia jasminoides J. Ellis, Eleocharis dulcis (Burm.f.) Trin. ex Hensch., and Achyranthes bidentata Blume (Figures 1 and 2). These CHM may have potential to become drugs for the treatment of DM by further exploring their hypoglycemic effects. We also found that some foods were used for treatment of DM in ancient times, and their hypoglycemic effects have been confirmed nowadays [15,16].

The mechanisms by which CHM treat diabetes include the following: (1) CHM increase insulin sensitivity and ameliorate insulin resistance; (2) CHM promote insulin secretion and elevate serum insulin levels; (3) CHM inhibit α-glucosidase activity; (4) CHM protect islet β cells and promote their regeneration; (5) CHM increase hepatic glycogen content and suppress gluconeogenesis; (6) CHM inhibit the secretion of glucagon; (7) CHM promote the glucose uptake by adipose and muscular tissues (Figure 4). Mechanisms of CHM treating diabetic complications include the following:
Table 2: Main mechanisms of CHM treating DM and its complications by nourishing Yin (Yang Yin) and benefiting vital energy (Yi Qi).

| Latin name                     | Family            | Extracts or monomers                     | In vivo/in vitro | Models                          | Effective doses/doses range | Mechanisms | Toxic effect | References |
|--------------------------------|-------------------|------------------------------------------|------------------|---------------------------------|------------------------------|------------|--------------|------------|
| *Liriope spicata* Lour.        | Liliaceae         | Crude polysaccharide, water extract      | In vivo          | BABL/c mice                     | 100, 200 mg/Kg              | IIAI       | NO           | [23]       |
| *Ophiopogon japonicus* (Thunb.) Ker Gawl. | Liliaceae | Polysaccharide                           | In vivo          | KK/AY mice, C57BL/6J mice       | 75, 300 mg/Kg               | IIAI       | ND           | [24]       |
| *Astragalus membranaceus* (Fisch.) Bunge | Leguminosae      | Polysaccharide                           | In vivo          | Ob/ob mice                      | 300 mg/Kg                   | IIAI       | ND           | [25]       |
| *Panax ginseng* C. A. Mey.     | Araliaceae        | Malonylginsenosides                      | In vivo          | Wistar rats                     | 50, 100 mg/Kg               | IIAI       | ND           | [31]       |
| *Panax pseudoginseng* Wall.    | Araliaceae        | Ginsenoside Rh2                          | In vivo          | Wistar rats                     | 1 mg/Kg                     | PIEI       | ND           | [32]       |
| *Porcelain*                    | Polyporaceae      | Crude extract                            | In vivo          | C57BL/KsJ-db/db mice, C57BL/6J mice | 1, 5, 10 mg/Kg             | IIAI       | ND           | [37]       |
| *Dioscorea oppositifolia* L.   | Dioscoreaceae     | Decoccted water                          | In vivo          | Wistar rats                     | 4 mg/Kg                     | IIAI       | ND           | [38]       |
| *Schisandra chinensis* (Turcz.) Baill. | Schisandraceae   | Lignan                                   | In vivo          | Kun Ming mice                   | 4.5 g/Kg                    | RAAR       | ND           | [39]       |
| *Stichopus chinensis*           | Clavicipitaceae   | Polysaccharide                           | In vivo          | BALB/c mice, SD rats            | 200, 400 mg/Kg              | PIEI       | ND           | [40]       |
|                                |                   | solid-state fermented mycelium            | In vivo          | KK/HIJ mice                     | 300 mg/Kg                   | PIPR       | ND           | [41]       |
| Latin name                      | Family             | Extracts or monomers | In vivo/ in vitro | Models                                      | Effective doses/doses range | Mechanisms | Toxic effect | References |
|--------------------------------|--------------------|----------------------|-------------------|--------------------------------------------|-----------------------------|------------|--------------|------------|
| *Cornus Officinalis* Siebold and Zucc | Cornaceae          | Methanol extract     | *In vitro*        | BRIN-BDI cells, H4IIE cells, Wistar rats, α-Glucosidase | 0–25 μg/mL, 20 mg/Kg, 1.2–2.1 μg/mL | PIEI, PIPR, IHSG | YES, cytotoxicity | [43] |
|                                |                    | Proanthocyanidins   | *In vitro*        |                                            |                             | INGA       | ND           |            |
| *Polygonatum odoratum* (Mill.) Druce | Liliaceae          | Total flavonoids    | *In vivo*         | Kun Ming mice, SD rats, SD rats            | 50, 100, 200 mg/Kg          | PIEI       | ND           | [44] |
|                                |                    | Flavonoid, saponin  | *In vivo*         |                                            | 500 mg/Kg                  | COSR, INGA | NO           |            |
| *Atractylodes macrocephala* Koidz. | Compositae         | Atractylenolide, amino acid | *In vivo* | Kun Ming mice | 1.8 g/Kg | RAAR        | ND           | [39] |
| *Codonopsis pilosula* (Franch.) Nannf. | Campanulaceae     | Saccharides, amino acid | *In vivo* | Kun Ming mice | 4.5 g/Kg | RAAR        | ND           | [39] |
| *Panax quinquefolius* L. | Araliaceae          | Ginsenoside         | *In vitro*        | Rat pancreatic β cell derived cell line, INS-1 | 5, 125, 250 μg/μL. | PIPR, PIEI | ND           | [47] |
| *Rehmannia glutinosa* Steud. | Scrophulariaceae   | Catalpol            | *In vitro*        | Wistar rats, THP-1 cells | 0.1 mg/Kg, 100, 300, 500 μmol | IHSG, COSR, BLIR | ND, NO      | [48] |
| *Dendrobium montiliforme* (L.) Sw. | Punicaceae         | Water extract       | *In vivo*         | NIH mice, SD rats | 125, 250, 500, 1000 mg/Kg | INSG, IHSG, PIEI | ND           | [49] |
| *Dendrobium chrysotoxum* Lindl. | Punicaceae         | Polysaccharide      | *In vitro*        | BALB/c mice, Mouse splenocytes, Jurkat cell, MCF-7 cells | 200, 500 mg/Kg, 0–200 μg/mL | COSR       | ND           | [50] |
| *Ganoderma lucidum* (Leys. ex Fr.) Karst | Polyporaceae       | Polysaccharides    | *In vitro*        | Albino Swiss mice, Wistar rat islets | 50, 100, 200 mg/Kg, 25–100 μg/mL | PIPR, COSR | NO           | [51] |

IIA: CHM increase insulin sensitivity and ameliorate insulin resistance; PIE: CHM promote insulin secretion and elevate serum insulin levels; INGA: CHM inhibit α-glucosidase activity; PIPR: CHM protect islet β cells and promote their regeneration; IHSG: CHM increase hepatic glycogen content and suppress gluconeogenesis; INSG: CHM inhibit the secretion of glucagon; PRGU: CHM promote the glucose uptake by adipose and muscular tissues. COSR: CHM control oxidative stress response, such as scavenging oxygen radicals, preventing lipid peroxidation, or inhibiting nitric oxide synthesis; RAAR: CHM regulate the activity of aldose reductase; BLIR: CHM block inflammatory response. NO means not toxic. ND means no data available. YES means toxic.
Table 3: Main mechanisms of CHM treating DM and its complications by clearing heat (Qing Re).

| Latin name                  | Family           | Extracts or monomers                        | In vivo/ in vitro | Models                                                                 | Effective doses/doses range | Mechanisms   | Toxic effect | References |
|-----------------------------|------------------|--------------------------------------------|-------------------|------------------------------------------------------------------------|-----------------------------|--------------|--------------|------------|
| *Paeonia x suffruticosa*    | Paeoniaceae      | Paeonol                                    | *In vivo*         | Newborn Wistar rats Intestinal brush border membrane vesicles, rat hepatoma cell line H4IIE, human skin fibroblasts cell line Hs68, mouse adipocytes 3T3-L1 | 200, 400 mg/Kg              | PRGU, INGA   | ND           | [53]       |
| *Morus alba* L.             | Moraceae         | 1-Deoxynojirimycin, polysaccharide         | *In vivo*         | ICR mice                                                              | 150 mg/Kg                   | IHSG, PIPR   | ND           | [56]       |
| *Momordica charantia* L.    | Cucurbitaceae    | Saponin fraction, lipid fraction           | *In vivo*         | Db/db mice                                                             | 150 mg/Kg                   | IIAI         | ND           | [57]       |
| *Pueraria lobata* (Willd.) Ohwi | Leguminosae    | Puerarin                                   | *In vivo*         | SD rats                                                                | 100, 200 mg/Kg              | IIAI         | ND           | [62]       |
| *Trigonella foenum-graecum* L. | Leguminosae    | Hydroalcoholic extract                     | *In vivo*         | C57BL/6J mice                                                          | 2 g/Kg                      | IIAI         | ND           | [64]       |
| *Gardenia jasminoides* J. Ellis | Rubiaceae      | Geniposide                                 | *In vivo*         | C57BL/6J mice                                                          | 200, 400 mg/Kg              | IHSG         | ND           | [67]       |
| Latin name                  | Family          | Extracts or monomers       | In vivo/in vitro | Models                                      | Effective doses/doses range | Mechanisms | Toxic effect | References |
|----------------------------|-----------------|----------------------------|------------------|---------------------------------------------|----------------------------|------------|--------------|------------|
| *Rheum palmatum* L.        | Emodin          | In vivo                    | 25, 50 mg/Kg     | 3 μmol/L                                    | PRGU                       | ND         | [68]         |
| *Acorus calamus* L.        | Araceae         | Crude ethanol extract      | Homozygous C57BL/ks db/db mice | 100 mg/Kg                                 | IIAI                       | ND         | [69]         |
|                            | Ethyl acetate fraction | In vitro                  | L6 rat skeletal muscle cells | 12.5, 25 μg/mL                            |                             |            |              |
|                            |                 |                            | ICR mice         | 400, 800 mg/Kg                             |                             |            |              |
|                            |                 |                            | HIT-T15 cell line | 0.41 μg/mL                                 |                             |            |              |
| *Eriobotrya japonica* (Thunb.) Lindl. | Rosaceae | Cinchonain-Ib | Wistar rats | 108 mg/Kg                                  | PIEI                       | ND         | [70]         |
|                            |                 |                            | Rat insulinoma cell line, INS-1 cells | 0.032 mg/ml |                             |            |              |
| *Anemarrhena asphodeloides* Bunge | Liliaceae | Timosaponin, anemaran Total saponins | Kun Ming mice | 1.8 g/Kg                                   | INGA                       | ND         | [39]         |
|                            |                 |                            | SD rats          | 200 mg/Kg                                  | BLIR                       | ND         | [72]         |
| *Lonicera japonica* Thunb. | Caprifoliaceae  | Chlorogenic acid, ginnol   | Kun Ming mice   | 2.3 g/Kg                                   | RAAR                       | ND         | [39]         |
| *Coptis chinensis* Franch. | Ranunculaceae   | Berberine chloride form    | Wistar rats, Beagle dogs | 125, 500, 250 mg/Kg, 80 mg/Kg | INGA                       | ND         | [73]         |
|                            |                 |                            | Caco-2 cells     | 2.5, 10, 40 mg/L                           |                             |            |              |
|                            |                 | Berberine                  | SD rats ventricular myocytes | 0.1-100 μmol/L                             | COSR                       | ND         | [74]         |
|                            |                 |                            | Wistar rats C57BLKS/J-Lepr<sup>db</sup>/Lepr<sup>db</sup> mice, | 100, 200 mg/Kg |                             |            |              |
|                            |                 | Berberine                  | Wistar rats 3T3-L1 cells, L6 cells | 5 mg/Kg |                             | IIAI         | ND         | [76]         |
|                            |                 |                            | 3T3-L1 cells, L6 cells | 380 mg/Kg |                             |            |              |
|                            |                 |                            | 3T3-L1 cells, L6 cells | 5 μg/mL |                             |            |              |
| *Potentilla discolor* Bunge | Rosaceae        | Flavonoids, triterpenoids  | Wistar rats     | 369, 501 mg/Kg                             | PIPR, COSR                 | ND         | [77]         |
| Latin name                              | Family          | Extracts or monomers | In vivo/ in vitro | Models                          | Effective doses/doses range | Mechanisms       | Toxic effect | References |
|-----------------------------------------|-----------------|----------------------|-------------------|---------------------------------|-----------------------------|------------------|--------------|------------|
| *Artemisia sphaerocephala* Krasch.      | Compositae      | *Artemisia sphaerocephala* Krasch. gum | *In vivo*         | SD rats                         | 0.3%, 0.9%, 2.7% gum         | IIAI, IHSG       | ND          | [78]       |
| *Sophora flavescens* Aiton              | Leguminosae     | Oxymatrine           | *In vivo*         | Wistar rats                     | 60, 120 mg/Kg               | COSR, BLIR       | ND          | [79]       |
| *Punica granatum* L.                    | Punicaceae      | Methanolic extract   | *In vivo*         | Zucker diabetic fatty rats, Zucker lean rats | 100–500 mg/Kg              | INGA             | ND          | [80]       |
| *Arctium lappa* L.                      | Compositae      | Arctigenin           | *In vivo*         | C57BL/6J mice, B6, V-Lep<sup>ob</sup>/Lep<sup>ob</sup> mice | 200, 25 mg/Kg               | IHSG, PRGU       | ND          | [81]       |

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Table 4: Main mechanisms of CHM treating DM and its complications by Wen Yang (tonifying Yang) or Hao Xue Hua Yu (activating blood circulation and easing congestion).

| Latin name                        | Family            | Extracts or monomers | In vivo/in vitro | Models                                                                 | Effective doses/doses range | Mechanisms                                                                 | Toxic effect | References |
|-----------------------------------|-------------------|----------------------|------------------|------------------------------------------------------------------------|----------------------------|----------------------------------------------------------------------------|--------------|------------|
| *Amomum xanthioides* Wall. ex Baker | Zingiberaceae     | Aqueous ethanolic extract | *In vitro*     | 3T3-L1 adipocytes                                                     | 0.02–0.5 mg/mL              | PRGU, IIAI                                                                  | ND           | [82]       |
| *Angelica hirsutiflora* Tang S. Liu, C. Y. Chao, and T. I. Chuang | Umbelliferae      | Methanolic extract  | *In vitro*      | ICR mice, HIT-T15 cells, human pancreatic islets                      | 10, 30 mg/Kg                | PIEI                                                                       | ND           | [83]       |
| *Ramulus cinnamomi* Lauraceae     | Cinnamaldehyde, benzyl benzoate | *In vivo*          | Kun Ming mice    | 1.4 g/Kg                                                               | COSR                        | ND                                                                         | [39]         |
| *Cinnamomum cassia* (Nees and T. Nees) J. Presl | Lauraceae         | Cinnamaldehyde, cinnamyl acetate, cassioside | *In vivo*      | Kun Ming mice                                                        | 700 mg/Kg                    | COSR                                                                       | ND           | [39]       |
| *Eucommia ulmoides* Oliv.         | Eucommiaceae      | Lignans, Water extract | *In vivo*      | Kun Ming mice C57BL/KsJ-db/db mice                                      | 1.4 g/Kg                     | COSR                                                                       | ND           | [39]       |
| *Ephedra sinica* Stapf            | Ephedraceae       | L-Ephedrine, alkaloid | *In vivo*      | RIN-m5F cells                                                         | 1.2 g/Kg 10–100 μg/mL      | PIPR, COSR                                                                  | NO <200 μg/mL | [85]       |
| *Zingiber officinale* Roscoe      | Zingiberaceae     | Phenolic gingerol   | *In vitro*      | L6 rat myoblast                                                        | 5–40 μg/mL                   | PRGU                                                                       | NO           | [86]       |
| *Acanthopanax senticosus* (Rupr. and Maxim.) Harms | Araliaceae        | Hot water extract, Polysaccharide | *In vitro*      | Db/db mice, Caco-2 cells, Wistar rats                                 | 500 mg/Kg 0.03–4 mg/mL, 200 mg/Kg | INGA, COSR                                      | ND           | [87], [88] |
| *Carica papaya* L.                | Caricaceae        | Aqueous extract     | *In vivo*      | Wistar rats                                                           | 0.75, 1.5 g/100 mL,        | PIPR, COSR, IHSG                                                             | ND           | [90]       |
| *Terminalia chebula* Retz.        | Combretaceae      | Chloroform extract  | *In vivo*      | SD rats                                                                | Short term study, 100, 200, 300 mg/Kg, Long term study, 300 mg/Kg | PIBER           | ND           | [91]       |
| *Epimedium brevicornum* Maxim.    | Berberidaceae     | Icarin              | *In vivo*      | SD rats                                                                | 80 mg/Kg                    | COSR                                                                       | ND           | [92]       |
| *Salvia miltiorrhiza* Bunge       | Lamiaceae         | Hydrophilic extract | *In vitro*     | HMEC-1 cells, human microvascular endothelial cells                   | 10 μg/mL                    | COSR                                                                       | ND           | [93]       |

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(1) CHM control oxidative stress response, such as scavenging oxygen radicals, preventing lipid peroxidation, or inhibiting nitric oxide synthesis; (2) CHM regulate the activity of aldose reductase; (3) CHM block inflammatory response. Furthermore, CHM hypoglycemic effects are mainly based on IIAI, PIEI, INGA, PIPR, PRGU, and IHSG and fewer CHM are based on INSG.

In addition, many modern clinical researches tended to focus on curative effects rather than underlying mechanisms. Although molecular biological, immunological, and phytochemical techniques have been widely applied to study the mechanism of CHM treating DM, the nature of many components or extracts was still not very clear.

5.2. Advantages of CHM in the Treatment of DM. Although CHM have many limitations, as aforementioned, the hypoglycemic effects of some CHM were well documented, and some can effectively ameliorate certain clinical symptoms of DM, such as polydipsia, polyuria, and polyphagia. A number of studies have shown that CHM or their extracts used in combination with western medicines work even better for the treatment of DM [19, 20]. For example, Trigonella foenum-graecum L. Saponin given together with sulphonylureas could effectively control the serum glucose, with few side effects, in DM patients whose serum glucose was not well controlled by oral administration of sulphonylureas [21].

5.3. Recommendations for Further Study of CHM for the Treatment of DM. CHM are increasingly used for the treatment of DM. However, some CHM also exacerbate some symptoms of DM such as polydipsia, polyuria, and polyphagia. Therefore, much more research is needed to develop new CHM or extracts that ameliorate DM symptoms without exacerbating them. Although modern clinical studies on CHM were rarely conducted or no information was available on the toxicity of CHM. Fourth, many modern clinical and experimental studies on CHM were methodologically defective, which reduces their reliability and validity. Chen et al. and Li et al.’s results also stated this limitation [17, 18].
of DM primarily because of increased awareness, on the part of patients and doctors, of their advantages, such as effectiveness, natural origin, and safety. However, in order to further extend their scope of application, the limitations of CHM should be avoided. More evidence-based clinical trials should be performed to substantiate the efficacy of CTM prescriptions and crude CHM for the treatment of DM. To confirm the effect of CHM on DM, larger-scale, multicentered, randomized, and controlled clinical trials are needed and statistical methods should be used in all clinical trials. Besides, the mechanisms of CHM and prescriptions should be examined at the molecular and cellular levels by fully taking advantage of the latest techniques, such as biochemical, biological, molecular biological, and immunological methods. Since adverse side effects associated with use of CHM, such as hepatotoxicity, nephrotoxicity and genotoxicity, were reported frequently, it is urgent to conduct toxicological studies on CHM. In order to achieve higher accuracy and better reproducibility, all studies on CHM should be conducted by following well-established and standardized procedures.

6. Conclusion

CHM used to and still play an important role in the treatment of DM in China and great progresses have been made over the last decades. A great many CHM monomer components possess antidiabetes actions. Therefore, it is of great significance to develop novel CHM for the treatment of DM and its complications. The underlying mechanism by which CHM treat DM are complicated and multifactorial and involve multiple organs; studying the effect of active monomer components of CHM might be a good starting point. It is strongly significant to pay close attention to CHM for treatment of DM and its complications.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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